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THE LANCET

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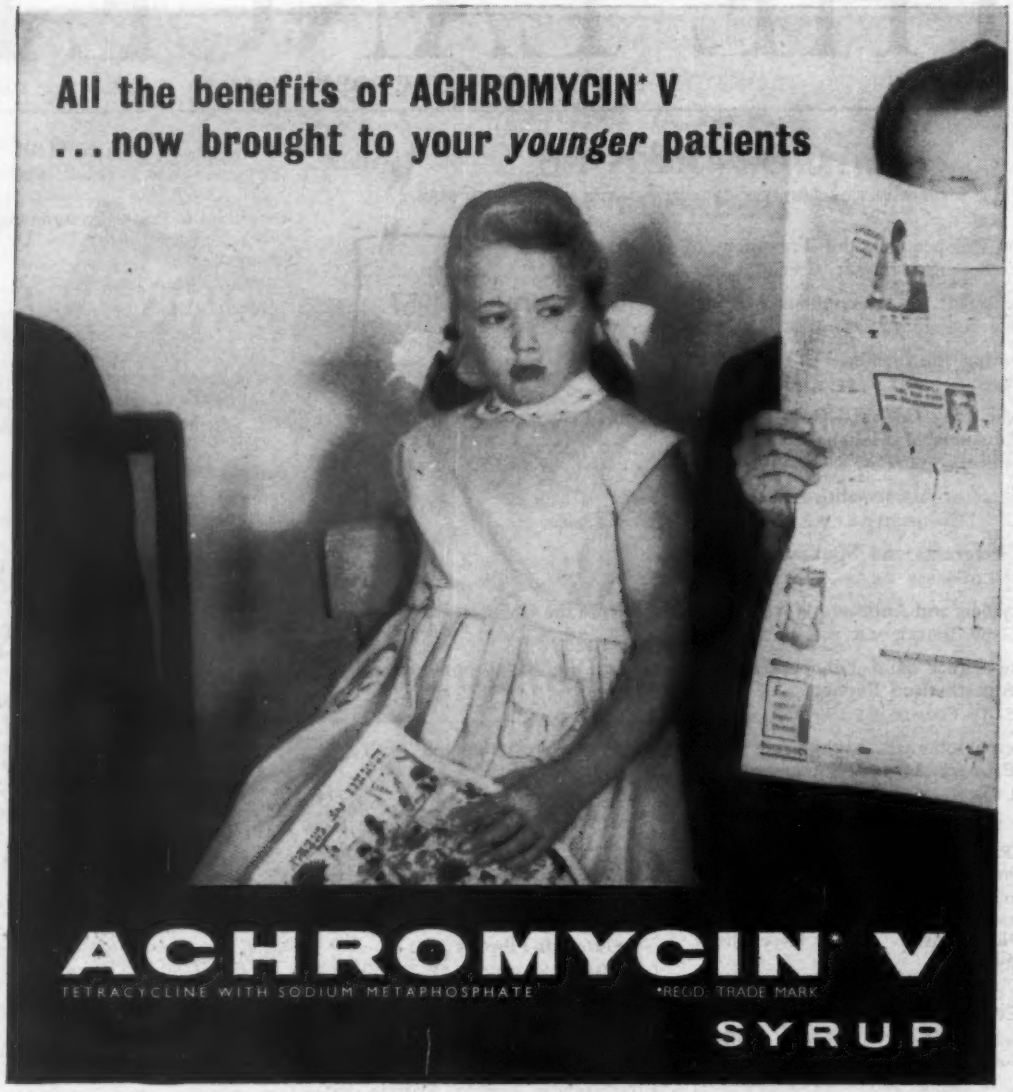

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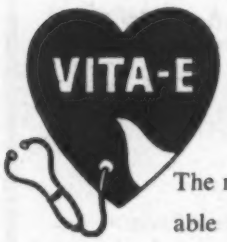

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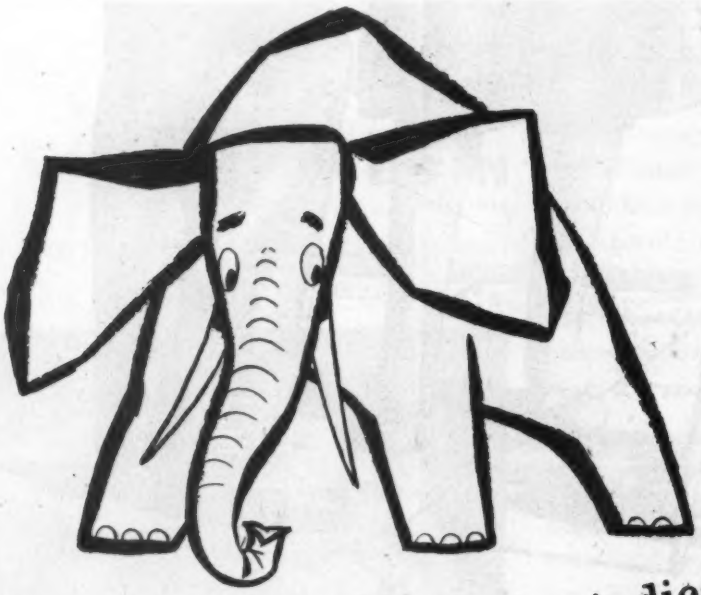

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(1954) 'Clinical Tests for Ketonuria', *'Lancet', April 17th, pp. 801/804*
(1954) '*Medicine Illustrated*', *May, p. 289*
(1954) '*Practical Clinical Biochemistry*', *Heinemann, p. 74*
(1954) 'Clinical Tests for Ketonuria', *'Lancet', July 10th, p. 95*

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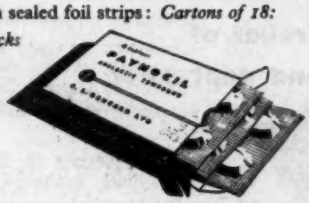

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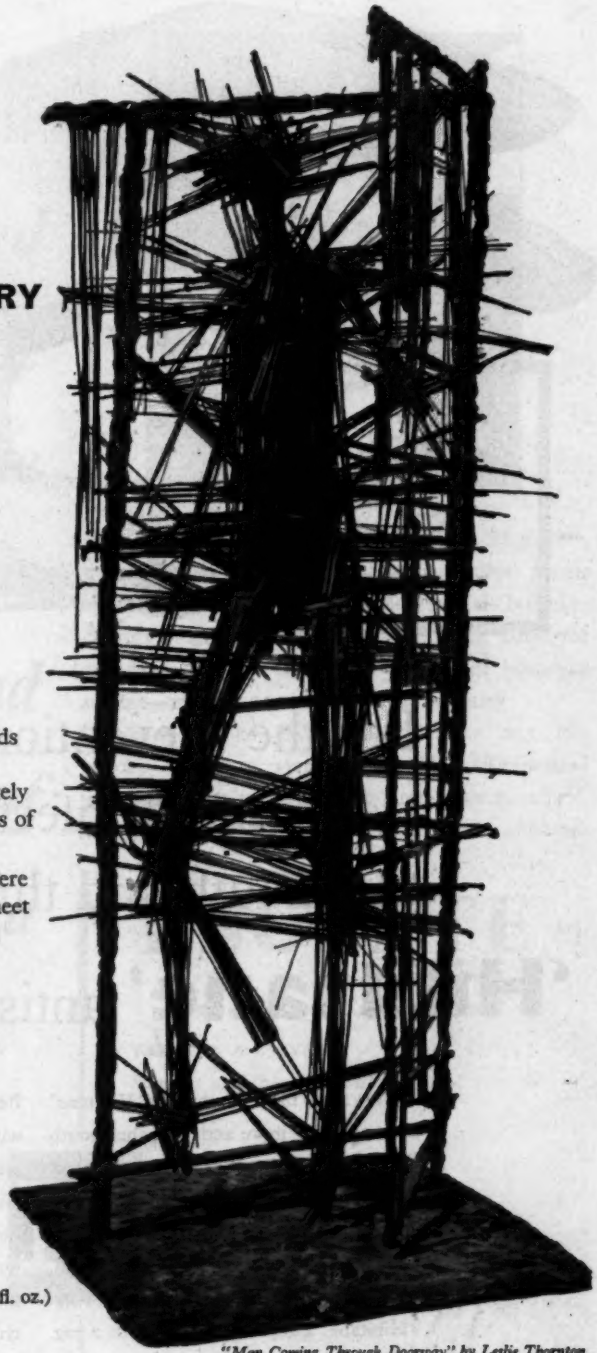

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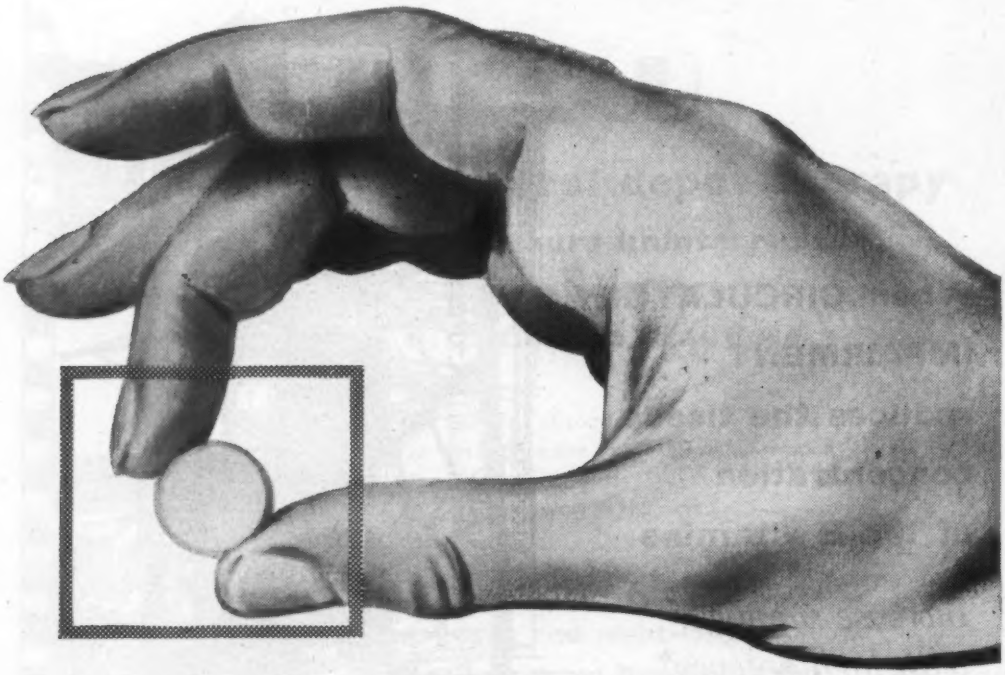

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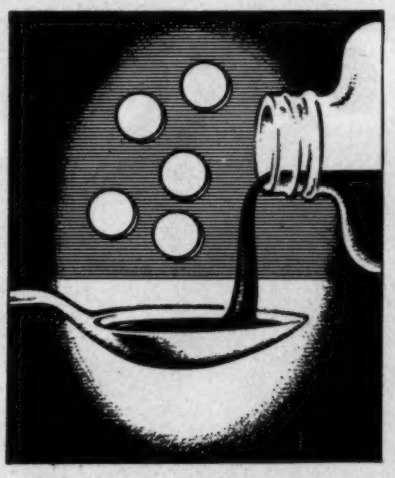

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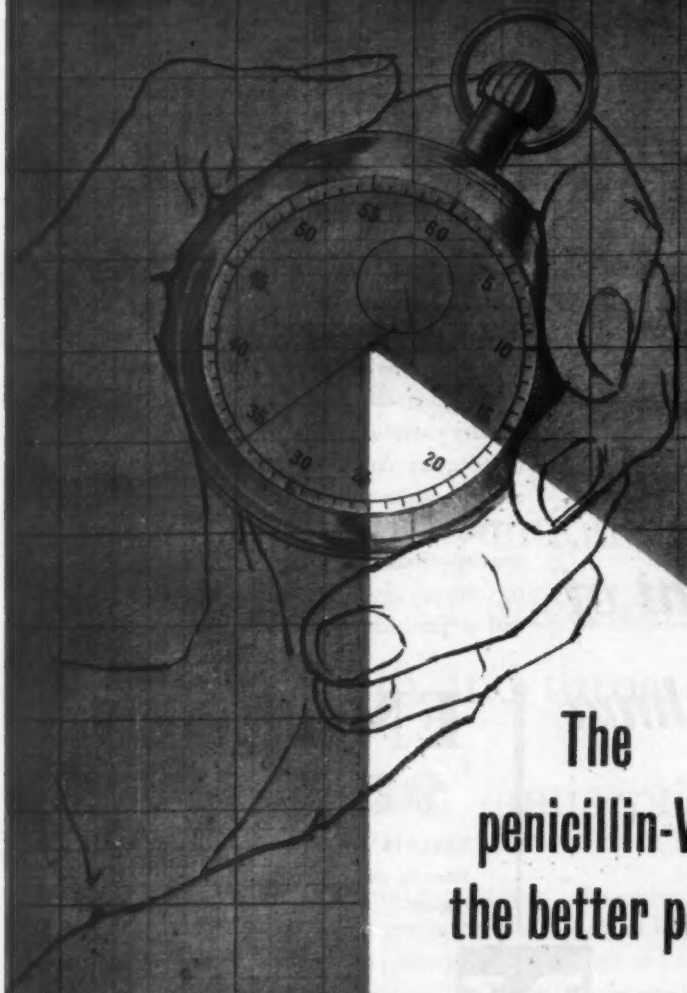

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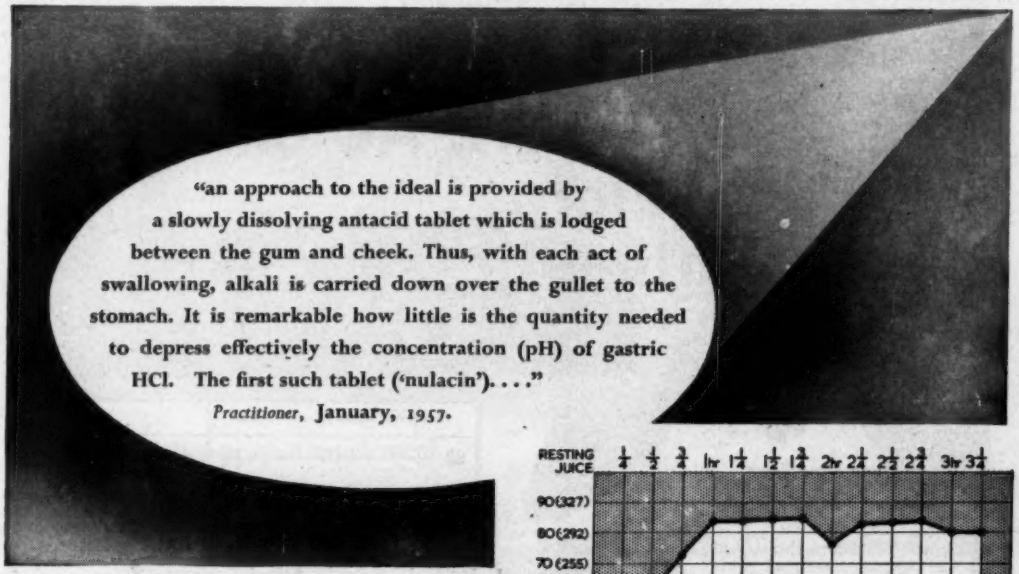

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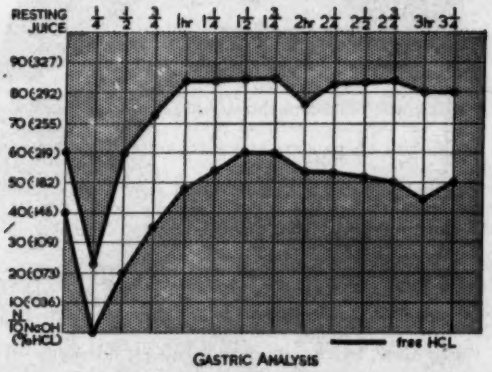

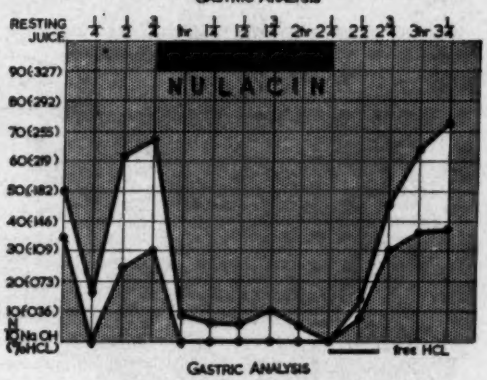

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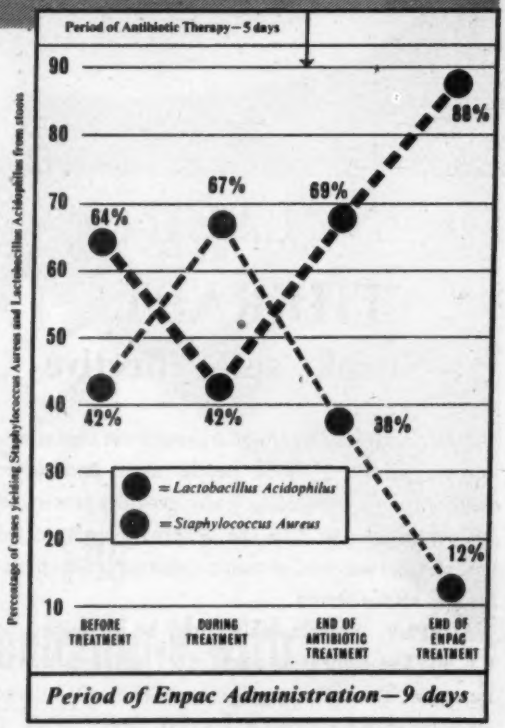

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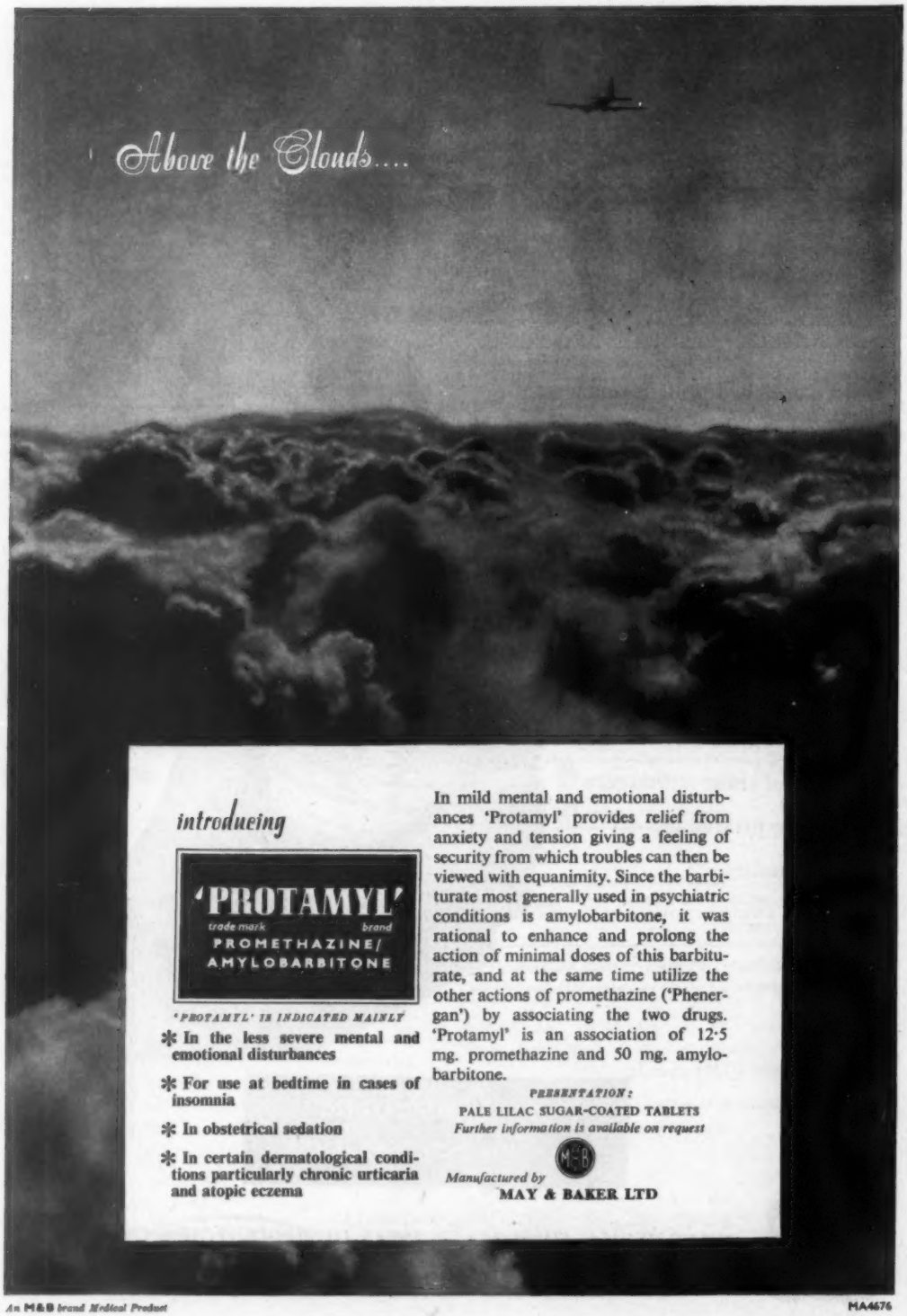

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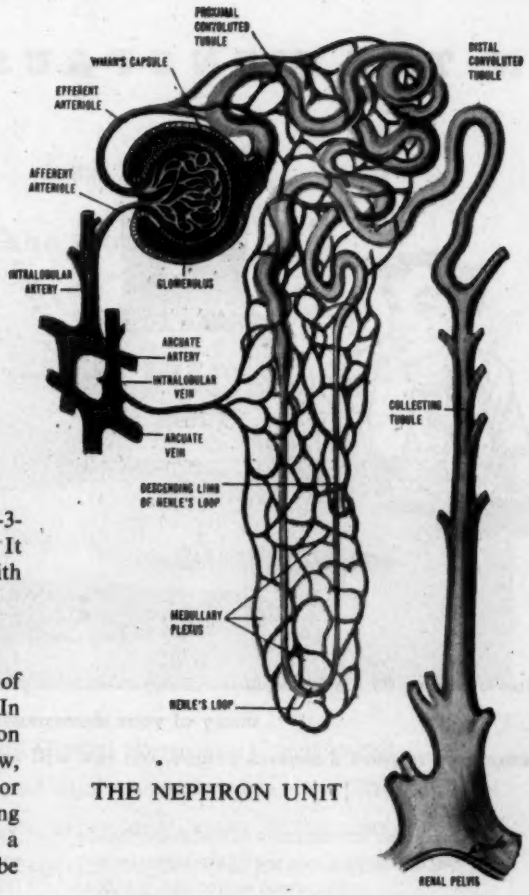

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1. *Wis. med. J.* (1954) **53**:322.
2. *Amer. J. Obstet. Gynec.* (1954) **8**:201.
3. *J. Indiana med. Ass.* (1954) **47**:899.
4. *J. Clin. Endocr.* (1954) **14**:272.

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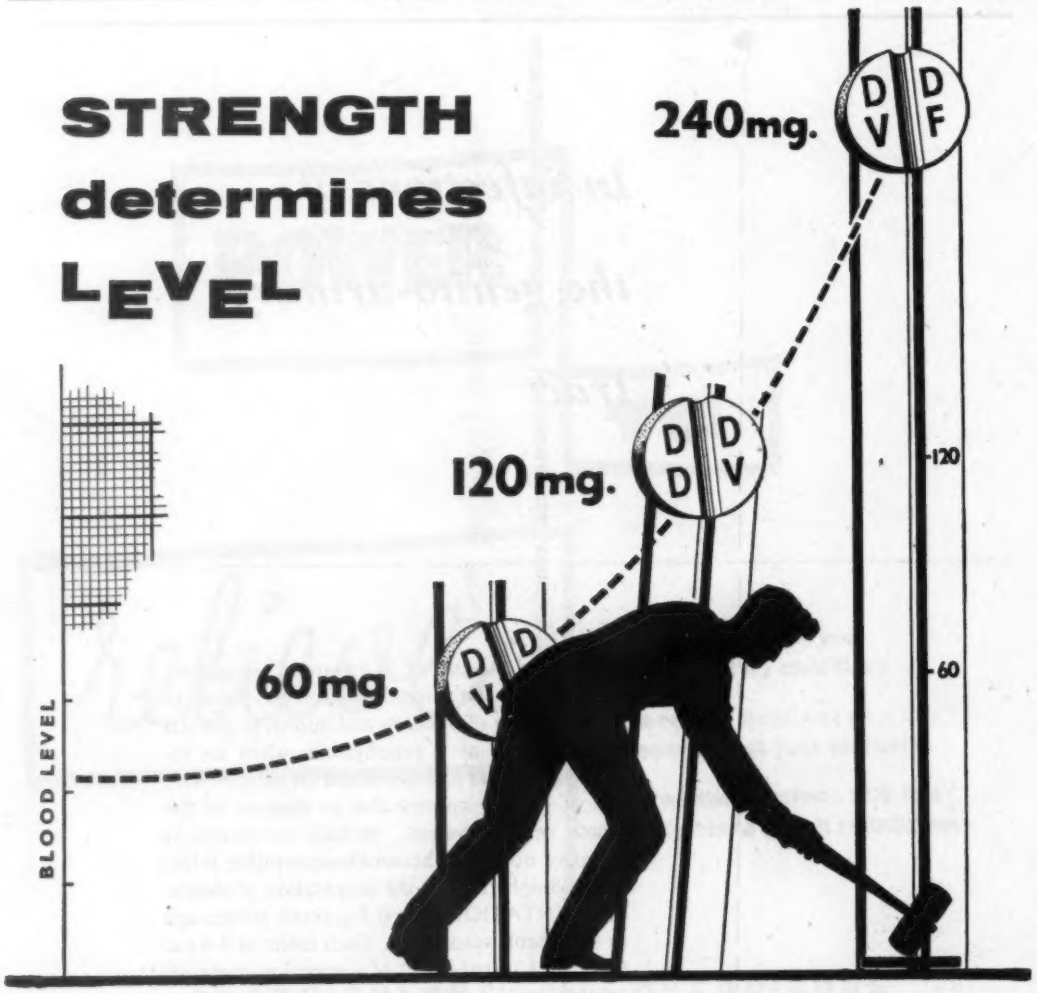

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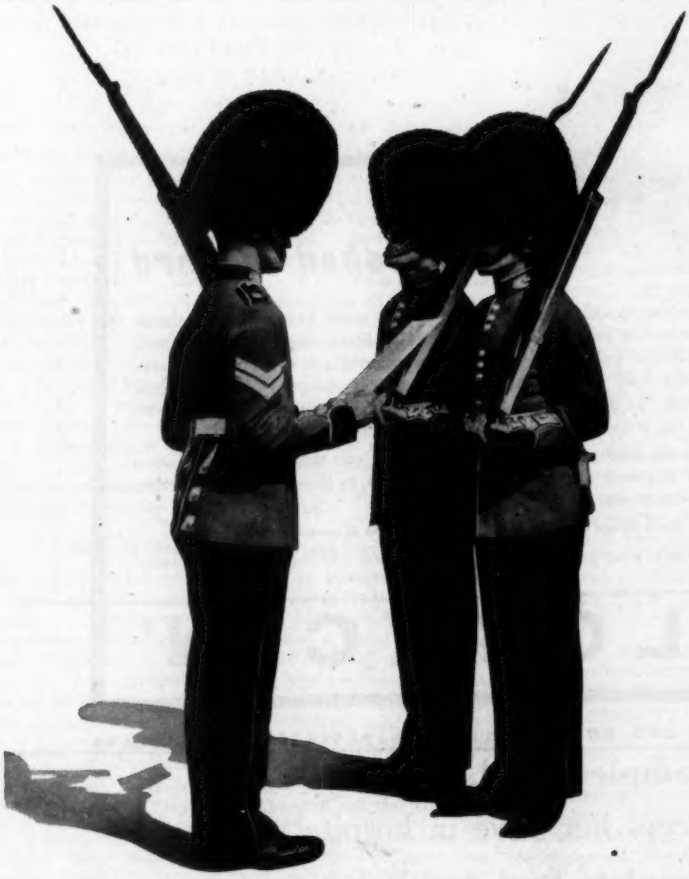

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NEW PROSPECTS IN THE TREATMENT OF HYPERTENSION*

I. McD. G. STEWART
M.D. Lond., M.R.C.P.
CONSULTANT PHYSICIAN, VICTORIA HOSPITAL, BLACKPOOL

IN 1732 Stephen Hales related to the council of the Royal Society the details of a new and singular experiment. He described how he had inserted a "brass pipe" into the left crural artery of a mare. To this pipe he had affixed a glass tube, finding then that "the blood rose in the tube 8 feet 3 inches perpendicular above the level of the left ventricle of the heart." With each pulse the blood rose and fell. These proceedings did not pass unnoticed by the mare herself. As Hales remarked, she grew "uneasy." Her pulse-rate became higher than he considered normal in a horse "not terrified nor in any pain." Whether the blood-pressure of a calm and happy horse might be less than 8 feet 3 inches he did not say. Indeed he could not. Nothing like this had ever been done before. It is perhaps of interest to us now to learn that, in effect upon the subject, this first measurement of blood-pressure was not unlike a good many million such estimations that have been made since.

What is Normal Blood-pressure?

This fundamental question was at once apparent to Mahomed, who, as a young registrar at Guy's Hospital, declared: "Before we can speak of a pulse as one of high pressure we must decide what is a pulse of normal pressure." Today we have to admit that the answer still eludes us. But of one thing we can be sure. By the influence of his thoughts alone, a man's blood-pressure can be made to vary by scores of millimetres of mercury. Here is a factor that must at once mock all attempts to set out an individual standard in terms of figures.

All the same, in group assessment, it seems that the sphygmomanometer may be able to sniff out the threat of disease at a very early stage. Pickering (1955) cites some interesting data culled from the experience of insurance companies by Dublin et al. (1949) (table I).

TABLE I—RELATION OF BLOOD-PRESSURE TO MORTALITY OF INSURED WHITE MALES—PER CENT. ACTUAL OF EXPECTED DEATHS, CLASSIFIED ACCORDING TO DIASTOLIC AND SYSTOLIC READINGS; BY AGES AT ISSUE 40–49, STANDARD AND SUB-STANDARD ISSUES COMBINED, EXPERIENCE FROM 1925 TO 1938 (DUBLIN ET AL. 1949)

Systolic pressure (mm. Hg)	Diastolic pressure (mm. Hg)						
	64-73	74-83	84-88	89-93	94-98	99-103	104-108
108-117 ..	..	..	94	..	..	..	..
118-127 ..	..	..	86	103	122	..	..
128-132 ..	93	95	98	103	107	..	..
133-137 ..	111	103	109	118	139	..	..
138-142 ..	121	119	130	146	170	166	..
143-147 ..	..	146	142	176	225	168	..
148-157 ..	..	204	196	212	223	304	411
158-167 ..	..	..	..	221	408	421	..

The mortality among insured white males is shown as a percentage of expected deaths, in relation to diastolic and systolic pressure-readings measured at the first examination, within four age-groups. Dublin et al. found "a significant increase in mortality with relatively moderate elevation of blood-pressure." A group of men aged 40–49 had average initial pressures of only 164 systolic and 96 diastolic mm. Hg; and this, moreover, when estimated under the disturbing influence of examination for life assurance. Taken casually, by their own doctors, the levels would surely have been lower still—in fact, well within that category of "hypertonia" which Evans (1957) claims to be a variation of the normal. Yet it was found that for the semen "the mortality from cardio-vascular-renal diseases was nearly four and a half times the average for all standard risks."

In his unique personal study of a thousand hypertensive patients followed over some twenty years Bechgaard (1957) has demonstrated the manner in which hypertensive mortality "falls with advancing age" being at all ages relatively much less in women. Old ladies, indeed, thrive, it seems, upon diastolic pressures up to 120 mm.Hg.

Perhaps, then, all that we can say of normality is that we should each adopt a standard technique of measurement, taking our readings after allowing our patients a brief fixed period of recumbency. Thus we can obtain a very rough but personal (and so valid), standard environment. We must know our patients, and ourselves, and the atmospheres that we create with each patient individually. We must bear in mind the many thousands of readings that we take with our own machine on patients whom we consider to be normal and abnormal, taking note how such figures relate to the interpretations of our colleagues, and to the further destinies of those same patients. Finally, it seems that, making an exception for elderly ladies, we should regard as most favourable pressures that, uninfluenced of course by any pathogenic cause of hypotension, are well below average on any occasion that we may chance to make the measurement. Whether we take this level to be "normal" is a matter of taste. All we can be confident of is that such patients, as a group, are less likely than their fellows to die of cardiovascular disease.

Ætiology as a Guide to Treatment

It has become customary to speak of hypertension as primary or secondary. These are misleading terms. The word "secondary" implies a sequence of cause and effect. Very rarely, however, does hypertension fall into any such identifiable relationship. An association there may well be—we see it in acute nephritis. Yet, as was precisely noted by Mahomed, here the blood-pressure rise precedes evidence of kidney damage. In no sense is the hypertension secondary. To my mind, therefore, it would seem better to designate the hypertensions of this type as "associated" rather than "secondary."

By the term primary, or essential, we mean that not even such an association is apparent to us. According to Pickering (1955) this form of hypertension does not deserve to be considered as a "specific disease entity." He deprecates the "long and futile search for a single specific cause," and goes on to say that, after many years work upon the problem it was, for him, "as though the veil had been lifted," when he came to realise at last that "the problem of the cause of essential hypertension is the problem of the cause of the variations of pressure in the population at large."

I must confess that the manner of this revelation has never been entirely clear to me. The relation between blood-pressure level and hypertensive disease does not follow a mathematical scale. It may well be that a raised blood-pressure, found upon even one occasion, should be taken as casting a shadow into the future. But the subject of such a finding is perfectly well. It is not yet certain that his prospect of survival is diminished. He is not suffering from essential hypertension. That grim label, as we use it, must surely imply engulfment, inexplicable and perhaps quite sudden, within an evil vortex of illness in which hypertension, of a degree sufficient to threaten cardiovascular complication *to the particular individual concerned* has become established. Here is a uniform event which would seem to proclaim, all too clearly, a defined and active malady. The moment of its onset is imperceptible, but that is not to deny its reality. In like manner we cannot define the exact moment at which darkness breaks into dawn, but between noon and midnight there can be no mistake. As for the alleged search

* Extract from the Buckston Browne prize lecture to the Harveian Society of London, Dec. 12, 1956.

for a "single specific cause," it must surely be many years since anyone thought of essential hypertension as a disease of single ætiology: heredity, age, sex, environment—clearly all are concerned. The plain fact remains, however, that despite much endeavour by the clinical scientists nobody yet can identify the exact nature and working of the causative factors.

Rationale of the Modern Treatment of Hypertension

What, then, if we know nothing of ætiology, is the basis of the improved prospects in treatment? It consists, of course, in the arbitrary reduction of raised arterial pressure by techniques designed to inhibit sympathetic maintenance of arterial muscle tone. The surgeons began it with sympathectomy. Now we have the new ganglion-blocking compounds. The value of all this, however, as an empirical method of treatment, can be assessed only against controls, and in the light of what we know of the natural history of the disease.

Prognosis and Cause of Death

Hypertensive patients do not live long. The gradings in table II are from the classification by Keith et al.

TABLE II—PERCENTAGE OF HYPERTENSIVE PATIENTS DEAD AT YEARLY INTERVALS AFTER FIRST EXAMINATION (KEITH ET AL., 1939)

Year	Grade			
	I	II	III	IV
1	10	12	35	79
2	20	23	67	88
3	30	38	78	94
4	30	42	78	98
5	30	46	80	99

(1939), based upon retinal appearances. Grade IV implies the "malignant" phase, with arteriolonecrosis and papill-œdema. Nearly all these patients are dead within a year. Even more significant, perhaps, is that fact that about half of the grade-II patients are dead within four years. Remember that, at their first examination, these patients had hypertensive changes only in the retinal arteries, the typical sausage-stringing, without exudates or hæmorrhage. Most died from cardiovascular disease in heart, brain, or kidney (table III).

These tables suggest that hypertension itself causes the vascular lesions. Much experimental evidence, including the classic demonstration by Wilson and Byrom (1939) of vascular lesions developing in the "unprotected" kidney, has pointed to the same conclusion. Moreover, for many years physicians have been aware that hypertensive retinal lesions tend to develop in direct ratio with the height of the pressure and the speed with which the rise is attained. Even more significantly they have noted that this process may be reversible.

Two Assumptions

All the evidence then, both experimental and clinical, would appear to justify two basic assumptions:

1. Hypertension disables and kills only through its secondary vascular effects.
2. Reduction of blood-pressure may arrest or postpone these effects.

From this we can formulate a rational basis for the modern treatment of hypertension: exclude the rarities of known causation (e.g., phæochromocytoma, coarctation of the aorta, and unilateral renal disease), then use any means to force down the abnormally raised blood-pressure. This will diminish the cardiovascular complications and so improve and prolong life.

The best criterion of success in treatment is survival. Now let us see what can be done with the new compounds.

TABLE III—CAUSE OF DEATH AT NECROPSY (SMITH ET AL., 1950)

Grade (Keith et al., 1939)	Total no. of cases	Cardiac failure (including coronary-artery disease)	Stroke	Uræmia	Unrelated
I	100	28	9	3	68
II	100	46	17	2	35
III	76	39	14	12	11
IV	100	22	16	59	3

Treatment of Hypertension by Ganglion-blocking Agents

Smirk (1954) first reported that after eighteen months 75% of patients with malignant hypertension treated with methonium compounds were alive, compared with 12% of a control series; later McMichael (1956), also using methoniums, found a five-year life expectancy of 50% in a group of malignant hypertensives with blood-urea initially below 60 mg. per 100 ml.; now Smirk (1956) has claimed a 57% survival in 44 such patients over a period of six years, compared with 1% in the untreated controls described by Keith et al.

We must next ask ourselves what influence these promising reports should exert on our management of patients who have not entered the malignant phase.

You will notice that I do not use the word "benign." This adjective was first used in connection with hypertension by Fahr, who sought to make a distinction in histopathology. In the light of what we know about prognosis in all patients whose blood-pressure remains considerably raised, and bearing in mind that in only some 2% of these does the disease ever become "malignant," I think you will agree that our readiness to accept the term "benign" as a clinical description of any form of hypertension reveals in our profession a remarkable incapacity to appreciate the meaning of words.

At once we find ourselves faced with some fundamental questions. Why, for example, if this technique of pressure-reduction has proved so effective in patients with largely irreparable cardiovascular damage, should it not be used in all patients with fixed hypertension? We know that it is the secondary effects which prove fatal. Why not cut short the hypertensive rise as soon as it be recognised? Would not this preclude the development of the fatal vascular lesions? These questions concern the comfort and capabilities, the peace of mind and survival, of millions of citizens in England alone.

Witts (1954), among others, has held that use of the new preparations should be restricted to patients with malignant hypertension or hypertensive encephalopathy. But this, surely, is to deny the fact that many other forms of hypertension, though technically not "malignant," constitute only a slightly less potent threat to life. Since the mechanism of the fatal process is fundamentally the same in all forms of hypertension, should we not then rather ask ourselves what reasons can there be for not seeking to lower the pressure of these patients also?

My own feeling is that there is only one serious objection—but this is formidable indeed. Treatment with the ganglion-blocking compounds demands the active co-operation of the patient, who thus has to be told all about his blood-pressure. Frequent sphygmomanometer readings are required during the first weeks, and regularly thereafter. This must impose a very serious anxiety burden, and we are bound to admit that, in applying this remedy, we must, at present, expose our patients to a psychological danger comparable with the physical threat. Somewhere, then, a dividing-line has to be found.

Evident Hypertensive Vascular Damage

In addition to the victims of malignant hypertension, there is another, much larger, category of hypertensive patients who should receive the new treatment. This includes most of those in whom hypertensive vascular damage is already apparent. Hypertensive left ventricular failure, encephalopathy with or without fits, and hypertensive renal damage are all manifestations which demand attack by forced reduction of blood-pressure, unless there be recent arterial thrombosis, incipient uræmia, or extreme old age, to contra-indicate it.

Smithwick and Thompson (1953) studied the effect of sympathectomy in patients of this type, and found evident improvement in survival-rates after surgery. Even better results from medical treatment with the new compounds are now beginning to appear. Smirk (1956) and his colleagues in New Zealand have already obtained a much increased survival in a six-year follow-up of 320 patients.

Most physicians, hitherto, have necessarily confined their attention largely to recording clinical progress. Opinion is universal that benefit is great. Cardiac failure can be overcome and dyspnœa reduced; heart-size tends to diminish and retinal changes to regress; more slowly electrocardiographic patterns of left ventricular strain incline to become less pronounced. McMichael (1956) believes that significant relief may also be afforded to the kidney. Smirk, indeed, maintains that "the prevention of strokes is the major problem remaining."

It would be a pity to claim too much. Shirley Smith and Fowler (1955), differing here from Smirk, thought that hypotensive treatment "could not take the place of digitalis and mersalyl in the initial treatment of congestive heart failure, but by controlling the pressure it might prevent a recurrence." This has been my own experience. Even one previous attack of pulmonary œdema persuades me, in general, to persist with digitalis and, for a time at least, with the intramuscular mercurial diuretics as well.

Gross Sustained Hypertension without Symptoms

It seems reasonable, then, to offer hypotensive therapy to most patients with overt cardiovascular lesions. Should it be used in any other circumstances? According to Pickering (1955), "patients requiring no specific therapy are in general those without symptoms . . ." May I emphasise, however, that symptoms are important only in so far as they indicate vascular damage. In hypertensive patients they are very often the produce of anxiety, deriving solely from knowledge of the raised pressure. Headache, for example, nearly always has this origin.

On the other hand the patient may be in grave peril without complaint of any kind. A young man of 35 may be found by chance, at a life-assurance examination, to have a resting diastolic pressure of 130 mm. Hg with a bad family-history of hypertensive disease; a few months later the pressure may have risen still further. Such a man may feel perfectly well. There may be no physical signs apart from the diastolic reading, and all the special investigations may be normal. Yet we can be sure that on a long-term view, even of a few years, he is in grave danger. Should we withhold effective therapy until vascular damage is evident?

Here the first step should be to observe the effect of bed rest. But if, despite rest and sedation, the pressure remains virtually unchanged, are we now to run the risk of changing a happy extrovert into an anxious creature constantly preoccupied with his blood-pressure?

My own feeling is that the answer should be Yes. Fully conscious of the significance of the step, the physician should explain simply that the blood-pressure is raised and must be brought down. The confidence and cooperation of the patient should be sought and effective hypotensive therapy begun, since the danger that his life will be spoiled by the knowledge of his condition is less than the calculated risk that it will be damaged and shortened unless something substantial be done. Perhaps one of the best of the new prospects in hypertension awaits patients of this type.

Moderate Sustained Hypertension without Symptoms

Logically it may be supposed that forced lowering even of moderate sustained hypertension should commonly prolong life in all patients short of old age, particularly in men. Solely on account of the anxiety factor such therapy is, however, probably best withheld for the present outside the groups that I have specified.

Let me add that no patient should be told about his blood-pressure unless treatment demanding his knowledge and cooperation be intended. So often, in a few words, we destroy for a lifetime the peace of mind of our patients while merely offering advice that could be given just as well without betrayal of its purpose.

All this is very far from saying that, short of autonomic paralysant therapy, no treatment is of any value. Change to a gentler tenor of life, weight reduction with carbohydrate and salt restriction, sedatives, encouragement and reassurance, with digitalis and mercural diuretics as required, all tend to lower pressure, to improve health, and no doubt to prolong life. They may be usefully employed, with pressure readings taken casually and seldom, in those middle-aged ladies in whom, for decades, hypertension does indeed remain almost "benign". Should the hypertension take a sterner turn, however, these resources alone will be powerless to arrest its inexorable progress.

Choice and Use of Drug

Only with the introduction of the ganglion-blocking agents was real progress made in the drug treatment of hypertension. Virtually they may be said to have supplanted surgery upon the sympathetic symptom. As yet no other drug can compare with them.

I say this fully aware of the present vogue for reserpine. The derivatives of the rauwolfia shrub have long been renowned in Hindu medicine as a remedy for madness, dysentery, insomnia, and various other not obviously associated maladies. Their hypotensive action, however, has appeared to me to be slight, and their depressive side-effect severe.

The virtue of the new compounds lies in their selective action on arterial tone, with influence on neuromuscular, cerebral, and renal function reduced to a minimum. During the past year or two it has been realised that, despite theoretical objection provoked by erratic blood-levels, they work very well when given by mouth. Thus they impose no great burden on the patient. Upon blood-pressure their influence is potent, practical, and reasonably predictable.

Extent of Pressure-fall to be Attempted

The object originally sought by many was a forced reduction to some hypothetically normal level. This, in a patient going about his daily affairs, I found to be impossible and the attempt dangerous. Fortunately, however, it soon began to appear that the improvements already described might be set in train, and great benefit accrue, without the need for any very profound lowering of the raised pressure.

Let me take as an example the first four patients with malignant hypertension that I treated with autonomic-paralysant drugs (table IV). All were middle-aged men. Preliminary investigation and treatment was done in hospital.

TABLE IV—MALIGNANT HYPERTENSION TREATED WITH PENTOLINIUM BY MOUTH

Patient	Age (yr.)	Presenting symptoms	Initial B.P. (mm. Hg)	Subsequent average standing diastolic pressure (mm. Hg)	Result
1	58	Severe visual defect; dyspnœa.	250/150	119	After 38 months, vision good. Full office work.
2	69	Severe visual defect.	225/140	118	Fatal stroke after 18 months. Vision had been much improved.
3	53	Severe visual defect; dyspnœa.	>260/180	113	After 36 months, vision much improved. Active business.
4	54	Severe visual defect; dyspnœa.	250/185	121	After 36 months, vision much improved. Full office work.

Renal function in each was fairly good. When first seen they all had gross papillœdema with severe visual defect. They were unable to read, and could recognise faces at a distance of no more than a few feet. Their diastolic pressures varied between 165 and 190 mm. Hg. In all there was clinical, radiographic, and electrocardiographic evidence of severe left-ventricular failure.

Now the essential point about these patients is, that by the standard of their blood-pressure levels alone the control achieved has been very poor. Despite high dosage, varied repeatedly under my own direct observation, the standing diastolic levels have seldom been below 115 mm. and often above 140 mm. Hg. Yet, after more than three years, 3 of these men continue active in their business, with good vision and no gross disability. In their ocular fundi a few hard macular exudates and slight residual blurring of the disc edges, together with the original spastic arterial changes, are all that remain of the original gross retinopathy. There has been corresponding cardiac improvement. The 4th man also did very well until he died suddenly of a stroke after eighteen months. Mortality figures of the type that have been quoted suggest that, without treatment, all 4 should have been dead at the end of about six months.

With the latest preparations it is becoming easier to obtain a smooth and more substantial response. Yet it would appear that even a limited depression of the blood-pressure is capable of achieving a clinical effectiveness comparable with that claimed by workers who have practised the most exacting control. It is as though some vicious circle can be broken. Realisation of this must greatly encourage our hopes for the future.

The Future

I have tried to formulate a set of principles as a guide to the treatment of hypertension with the new hypotensive agents. Our present ideas about the selection of patients are likely to change rapidly. Already we can claim that the value of the method is no longer wholly uncontrolled. With the " malignant " phase, indeed, the control is good and here the results of the new therapy, judged by the ultimate criterion of survival, have been shown to be excellent. With severe hypertension short of " malignancy", the evidence of controlled clinical observation points decisively in the same direction. Admittedly we have as yet no control with uncomplicated hypertension. Nevertheless, the findings of life-assurance companies must lead us to suppose that any sustained rise of arterial pressure occurring short of old age, particularly in men, presents a grave long-term threat—and this in consequence of that very mechanism of vascular damage that we can see halted in its later stages by forced reduction of arterial pressure.

Is there not, therefore, a case for a controlled trial of the new agents with every degree of established hypertension ? Might not life be thus sometimes greatly prolonged, perhaps for decades ? If such immense benefit could be proved, might not the whole climate of professional and public opinion undergo a salutary change ? Would there not then be a hope that the act of revealing to the patient the fact of his hypertension need not inevitably release a flood of anxiety symptoms ?

Perhaps soon we shall be provided with a tablet that we can rely on to hold down pressure gently and evenly for twenty-four hours. The difficulty then will be to persuade people to take the thing regularly, yet without alarm, when all the time they feel perfectly well.

Such are the possibilities that face us in the immediate future. They open a cheerful prospect. Some day perhaps the clinical scientists will reveal for us the ultimate causes of hypertension. In the meantime, for the first time since Stephen Hales so alarmed his horse, there is appearing real hope of lasting benefit for many thousands of men and women whose lives hitherto have been under constant threat of death or damage.

Summary

Hypertensive disability and death are caused by the secondary vascular lesions.

Arbitrary reduction of blood-pressure can delay or arrest these lesions.

A relatively slight fall in pressure may suffice.

For this purpose the ganglion-blocking agents given by mouth are potent, practical, and reasonably predictable in their effect.

In view of the grim prognosis it seems reasonable that the use of this technique should be extended eventually to most forms of established hypertension.

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TREATMENT OF TUBERCULOUS MENINGITIS

A COMPARATIVE TRIAL

BY

A SCOTTISH JOINT COMMITTEE *

THE problem of the best way to use the different forms of chemotherapy now available in tuberculous meningitis still requires attention. Continued study of varying patterns of treatment is desirable not only with a view to determining whether one is more effective than another, but also in order to reduce the discomforts to which the patient is subjected when treatment involves the use of injections, especially by the intrathecal route. This combined Scottish study was planned as a result of the suggestion made by Anderson et al. (1953) that a marked reduction in the use of intrathecal medication with streptomycin did not diminish the efficiency of chemotherapy.

Material and Methods

Cooperating Units

Table I indicates the centres which took part in the trial and the numbers of cases treated at each. These are the main receiving units in their districts, and in all of them patients are accepted for admission without previous selection. The first patients were admitted in July, 1953, and the last in June, 1955. The minimum period of surveillance at the time of final review (March, 1957) is therefore one year and nine months.

Administrative Arrangements

Special case-sheets were prepared and methods of recording were standardised by a previous definition of terms. All the patients underwent a careful clinical examination, which included Mantoux testing and radiographic studies. Bacteriological confirmation of the clinical diagnosis was sought by systematic examination of initial specimens of cerebrospinal fluid (C.S.F.) by direct microscopy, by culture, or by guineapig inoculation. The cellular, protein, and sugar content of the C.S.F.

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TABLE I—NUMBER OF CASES TREATED AT EACH CENTRE

Hospital	No. of cases
Ruchill (Glasgow)	51
Belvidere (Glasgow)	26
Southfield (Edinburgh)	14
King's Cross (Dundee)	10
Knightswood (Glasgow)	5
Gateside (Greenock)	5
Total	111

was estimated on admission and weekly during the course of treatment. At the time of this weekly lumbar puncture an assessment of the clinical condition was made and recorded on a special summary form.

Definition of Treatment Groups

Cases were allocated by random selection to three treatment groups in the following way. When it was decided to include a patient in the trial, a numbered envelope was opened and a card withdrawn which indicated the form of treatment to be adopted. 198 of these envelopes were prepared at the start of the trial, containing equal numbers of cards representing the three forms of treatment. These were divided in random fashion among the different centres. The three schedules of treatment were :

Standard group.—This group was given streptomycin intramuscularly and intrathecally. Treatment was continued for at least six months with intramuscular streptomycin in daily doses of 1 g. for adults and proportionally smaller amounts for children. Intrathecal therapy was given daily for twenty-eight days in a dose of 100 mg. or less, according to age. Thereafter intrathecal injections were given three times weekly, twice weekly, and once weekly for consecutive periods of four weeks each. Throughout, *p*-aminosalicylic acid (P.A.S.) was given orally in a maximum dose of 15 g. daily. Isoniazid therapy was deliberately withheld, at least for eight weeks from the start of treatment.

Isoniazid group.—Isoniazid and P.A.S. were administered throughout the entire period of therapy. Isoniazid was administered in a dose of approximately 10 mg. per kg. of body-weight daily to a maximum of 500 mg. daily. The dose of P.A.S. was the same as that used in the Standard Group. During the first week of treatment patients received streptomycin daily by intramuscular and intrathecal injection, in the same dosage as in the Standard Group. Thereafter no streptomycin was given ; hence for this group isoniazid and P.A.S. were the sole forms of chemotherapy for all but the first week of the treatment course. Treatment was continued for at least six months.

Compromise group.—During the first week the treatment was the same as in the Isoniazid Group. Throughout the remainder of the period of treatment the patient was given isoniazid and P.A.S. as in the Isoniazid Group, with the addition of two doses of streptomycin weekly by both the intramuscular and the intrathecal routes. The dosages of streptomycin used were as in the Standard Group. Treatment was continued for at least six months.

The participating clinicians agreed that they would persist in the allocated treatment for at least eight weeks. At the end of this time each clinician was free to make such changes as he might consider desirable.

TABLE II—COMPARISON OF THREE TREATMENT GROUPS AS REGARDS AGE-GROUP AND CLASSIFICATION OF DISEASE

Age-group (yr.)	Standard group			Isoniazid group			Compromise group			Total
	E	I	A	E	I	A	E	I	A	
0–2	0	2	0	2	2	1 (1)	1	1	3 (2)	12 (3)
3–5	0	0	3 (2)	2	3	3 (1)	2	4	1	18 (3)
6–10	4	6 (1)	0	3	6 (1)	2	1	4	0	26 (2)
11–15	1	3	0	0	2	1	0	1 (1)	0	8 (1)
16–20	0	5 (3)	0	1	3	1	5	2 (1)	2 (1)	19 (5)
21 or more	0	4 (2)	2	0	7 (1)	4 (2)	3 (1)	6	2 (1)	28 (7)
Total	5	20 (6)	5 (2)	8	23 (2)	12 (4)	12 (1)	18 (2)	8 (4)	111 (21)
		30			43			38		111

Numerals in parentheses denote deaths.
E, early. I, intermediate. A, advanced.

Results

Similarity of Treatment Groups

The total series is 111, of which 30 were in the Standard Group, 43 in the Isoniazid Group, and 38 in the Compromise Group. The difference between the totals is explained partly by the exclusion of cases started on treatment without confirmation of the presence of tuberculous meningitis, and in which such confirmation was not obtained, and partly by the fact that the total of 198 cases at which we aimed originally could not be reached in a reasonable time. Towards the summer months of 1955 the numbers of admissions of tuberculous meningitis had fallen considerably, and it was decided to close the trial with the numbers then on the list.

TABLE III—COMPARISON OF THREE TREATMENT GROUPS IN RESPECT OF OTHER CHARACTERISTICS

Characteristic	Standard group	Isoniazid group	Compromise group	Total
Close family contact with tuberculosis	9	15	11	35 (32%)
Radiographic evidence of pulmonary or miliary tuberculosis	15	33	29	77 (70%)
Tuberculous lesion (other than pulmonary)	1	4	3	8 (7%)
Choroidal tubercles	3	5	6	14 (13%)
M. tuberculosis present in Smear	20 (66%)	30 (70%)	29 (76%)	79 (72%)
M. tuberculosis present in Culture	19	24	18	61
M. tuberculosis present in Guineapig	17	23	19	59
Total confirmed bacteriologically by one or other method	27	42	38	107
Total	30	43	38	111

Table II shows the subdivision of the three groups in respect of age-distribution and classification of stage of illness on admission. (The cases were classified according to the descriptions originally used in the Medical Research Council trial (1948).) In what is a comparatively small series it could not be expected that the groups would prove identical. Table II shows that the Isoniazid and the Compromise Groups contained an excess of patients in the younger age-groups and, therefore, of those classified as advanced. Such distributions have at least this advantage—that they are not favourable to the forms of treatment under test.

The data supplied in table III show that, although the three groups cannot be regarded as equivalent, there is again no evidence that the Isoniazid or Compromise Groups represented a less severe form of meningitis. It will be noted that in 4 patients bacteriological support for the diagnosis was not obtained. In each of these the clinical record and other information left no doubt that the diagnosis of tuberculous meningitis was correct.

Effect of Treatment

Mortality.—There were 21 deaths in the series, representing a mortality-rate of 19%. Of these deaths, 8 were in the Standard Group, 6 in the Isoniazid Group, and 7 in the Compromise Group. The distribution of the deaths in respect of age and clinical classification has been included in table II. So far as age is concerned, there is an excess of deaths among the youngest and

oldest age-groups in each of the treatment groups—a finding which accords with general experience. As regards the classification on admission, only 1 death occurred among the 25 classified as early; 10 among the 61 classified as intermediate; and 10 among the 25 advanced cases. Comparison of the treatment groups suggests that there was little difference between them as regards outcome. It is worth drawing attention to the fact that 15 patients died within twenty-eight days of admission to hospital (Standard Group 5, Isoniazid Group 5, and Compromise Group 5). This is important in confirming that each group contained a reasonable proportion of severe cases but also is of value in indicating that the treatment groups which received minimal intrathecal injections did not experience an excess of early deaths as a result of the reduction in intrathecal medication. The precise causes of death and duration of illness of those who died are listed in table IV.

TABLE IV—ANALYSIS OF DEATHS IN THREE TREATMENT GROUPS

Treatment group and no.	Classification	Age (yr.)	Duration till death (days)*	Remarks
Standard:				
1	I	18	40	Became increasingly drowsy, left hemiplegia, coma. No P.M.
2	I	23	7	Rapid deterioration. P.M. extensive tuberculous bronchopneumonia
3	I	7	63	Persistent vomiting. P.M. communicating hydrocephalus
4	I	25	2	Sudden deterioration. P.M. extensive tuberculous meningitis
5	I	18	26	Right hemiplegia, spinal block. P.M. extensive miliary tuberculosis, caseating focus left apex, communicating hydrocephalus
6	I	17	21	Left hemiplegia, quadriplegia. P.M. terminal pneumonia, gross meningitis
7	A	3	4	Rapid deterioration. No P.M.
8	A	2	38	Steady deterioration. No P.M.
Isoniazid:				
1	I	7	240	Developed thalamic obesity, sudden death. P.M. large tuberculoma
2	I	54	20	Bilateral pulmonary tuberculosis, steady deterioration. No P.M.
3	A	44	19	Hemiplegia. No P.M.
4	A	2⅔	15	Steady deterioration. No P.M.
5	A	1⅔	3	Extensive miliary tuberculosis. No P.M.
6	A	21	28	Steady deterioration, right hemiplegia. No P.M.
Compromise:				
1	E	27	39	Sudden change 19th day. P.M. extensive cerebral hemorrhage, little evidence of residual meningitis
2	I	14	26	Developed right hemiplegia. No P.M.
3	I	20	3	P.M extensive bilateral pulmonary tuberculosis with cavitation
4	A	4/12	22	Convulsions, hyperpyrexia, coma. No P.M.
5	A	30	109	Sudden deterioration, coma. P.M. hydrocephalus
6	A	10/12	3	Left hemiplegia. No P.M.
7	A	20	19	Coma throughout. P.M. congenital tricuspid atresia

* Duration till death = time from onset of treatment.
P.M., post-mortem examination. E, early. I, intermediate. A, advanced.

Relapse

Relapse was observed in 3 patients:

(1) Male, 12 years. Intermediate. Initial treatment group Standard. Recovery without complication. Dismissed after thirty-seven weeks, when chemotherapy was stopped. Relapsed after a year. Lymphocytic pleocytosis without symptoms or physical signs. Treated with intramuscular streptomycin and oral isoniazid and P.A.S. Remained well during his six months in hospital and for the nine months since his second dismissal.

(2) Male, 6 years. Intermediate. Initial treatment group Standard. Recovery without complication. Relapse immediately after completion of initial six months' course. Treatment as in Isoniazid Group for eleven months. Developed spinal block. Dismissed after seventeen months in hospital, well. Readmitted in second relapse eleven months later. Relapse on this occasion treated with streptomycin and isoniazid. Remains in hospital at present.

(3) Female, 2½ years. Intermediate. Initial treatment group Isoniazid; chemotherapy stopped at six months. Discharged home well and uncomplicated after forty-seven weeks in hospital. Readmitted after a year with relapse of meningitis and reappearance of miliary lesions in lung radiograph. Treated with streptomycin and isoniazid with recovery. Dismissed after forty-four weeks. Has remained well for nine months up to date.

In a 4th patient (female, 10 years) who was included in the Isoniazid Group, an increase in the C.S.F. cell count was observed at routine lumbar puncture at the end of the sixth month. Treatment was reinstituted but was discontinued after ten days because of the obvious well-being of the patient and the rapid return of the C.S.F. to normal. This patient is not regarded as having relapsed.

There was, therefore, no relapse among the patients in the Compromise Group, and only 1 true relapse among those in the Isoniazid Group.

Complications

Table V describes the complications encountered, from which it will be seen that many of these were present on admission and transient. The residual complications in the three groups were of similar type. The Isoniazid and Compromise Groups had a higher proportion of complications than the Standard Group (37%, 31%, and 23% respectively), but this may be due to the fact that these two groups contained an excess of cases in an advanced stage of illness on admission. Of the transient complications spinal block was recorded most often, and facial paralysis was common. Residual complications included partial or complete limb paralysis in 9 cases, mental retardation in 4, visual upset in 3 (of whom 1 was completely blind), and deafness in 1.

Duration of Abnormality of C.S.F.

Table VI compares the three treatment groups as regards the average duration of abnormal findings for cells, sugar, and protein. In compiling these figures deaths, of course, were excluded. In a few instances the C.S.F. was still abnormal at six months, and these cases have also been excluded. The figures are therefore presented with reservations, recognising that they are obtained from small totals. They may be accepted as indicating a trend. It will be observed that in the Isoniazid Group the C.S.F. returned to normal a little earlier than in the others. It will be recalled that it was this group in which all intrathecal medication was discontinued after one week, although lumbar puncture was performed weekly thereafter for progress studies as in the other two groups. The curtailment of injections of streptomycin might be expected to reduce the amount of meningeal irritation.

Duration of Stay in Hospital

No useful conclusions can be drawn from such figures in view of the fact that the minimum period of stay in hospital was six months, and except in 1 case (where the patient dismissed herself irregularly) this period was

TABLE VI—DURATION OF C.S.F. ABNORMALITIES IN TREATMENT GROUPS

Constituent	Duration (weeks)		
	Standard group	Isoniazid group	Compromise group
Cells	25·5	18·8	20·6
Sugar	16	11	13
Protein ..	21	15	21

The figures are averages for those patients whose C.S.F. returned to normal before dismissal.

exceeded by some weeks. The average durations of stay for the three treatment groups were: Standard Group, thirty-eight weeks; Isoniazid Group, thirty-four weeks; and Compromise Group, thirty-four weeks.

Changes in Therapy

All the patients were kept on the allocated treatment for eight weeks. Thereafter, if progress was considered unsatisfactory, treatment could be altered at the discretion of the clinician in charge of the case. The treatment changes recorded were as follows:

Standard Group:	Total number given additional therapy ..	13
	given isoniazid	8
	given increased dosage P.A.S.	5
Isoniazid Group:	Total number given additional therapy ..	10
	given streptomycin (usually intrathecally)	7
	given increased dosage isoniazid	3
	given increased dosage P.A.S.	4
Compromise Group:	Total number given additional therapy	6
	given streptomycin (usually with increased frequency)	4
	given increased dosage isoniazid	6
	given increased dosage P.A.S.	6

It will be observed that the greatest number of changes was made among the patients on Standard therapy. This can be explained perhaps by a natural apprehension that, in this group, which was not receiving isoniazid, any seeming slowness in recovery would be attributed to its absence. These changes in treatment must seem to detract from the value of the trial, but it is difficult to see any way in which they could be avoided in dealing with an infection of such severity.

Toxic or Other Side-effects of Treatment

Side-effects are listed in table VII for the three groups. The only unusual ones were encountered in those patients receiving isoniazid: 4 patients developed a peripheral neuritis, and 1 had transient blurring of vision and incapacity to accommodate. The occurrence of neuropathies with isoniazid has, of course, been observed by others (Biehl and Nimitz 1954, Katz et al. 1954, Dixon et al. 1956). It has been suggested that the administration of this chemical in very high dosage should always be allied with a high intake of pyridoxine. None of the patients in this series was given pyridoxine.

TABLE VII—TOXIC OR OTHER SIDE-EFFECTS OF TREATMENT

Standard group	Isoniazid group	Compromise group
Severe vomiting (P.A.S.) 4	Vomiting or diarrhœa (P.A.S.) 8	Vomiting (P.A.S.) 5
Sensitisation (streptomycin) 1	Sensitisation (P.A.S.) 2	Sensitisation (P.A.S.) 1
Deafness (streptomycin) 2	Visual disturbance (isoniazid) 1	Impairment of hearing (streptomycin) 1
	Peripheral neuritis (isoniazid) 2	Peripheral neuritis (isoniazid) 2

Discussion

The primary objective of the trial was to find if the reduction or elimination of intrathecal therapy made any difference to efficiency of chemotherapy in tuber-

TABLE V—COMPLICATIONS IN THREE TREATMENT GROUPS

Treatment group and no.	Classification	Age (yr.)	Complications	
			Transient	Residual
Standard:				
1	I	6	Left facial paralysis	Nil
2	I	12	Leg contractures	Nil
3	I	9	None	Mental retardation
4	I	17	None	Right 6th nerve paralysis
5	I	17	None	Mental retardation, but this was previously present
6	A	21	Spinal block	Paralysis both legs; deafness
7	A	2½	Right hemiplegia	Weakness right arm and leg
Isoniazid:				
1	E	16	Bilateral ptosis	Nil
2	E	3½	None	Left hemiplegia
3	I	17	Right hemiplegia noted for 2 days	Nil
4	I	4½	None	Weakness right arm and leg, blindness, tuberculomata removed from left parietal region
5	I	5	Spinal block	Nil
6	I	1	Partial spinal block	Nil
7	I	6	Left hemiplegia, left strabismus	Weakness left hand
8	I	46	Left facial palsy, paralysis of bladder	Nil
9	I	2	Spinal block	Nil
10	A	24	Left facial palsy	Nil
11	A	2	Spasticity of legs	Nil
12	A	16	Spinal block	Nil
13	A	15	Spinal block	Left facial paralysis, left hemiplegia
14	A	2	Blind from 9th to 36th day	Nil
15	A	27	Spinal block	Nil
16	A	10	Strabismus left eye	Left hemiplegia, improving
Compromise:				
1	E	17	None	5½ mos. after onset of treatment left 6th nerve paralysis, double vision
2	E	17	3rd nerve paralysis	Nil
3	E	16	Left facial paralysis	Nil
4	E	1	Right hemiplegia	Weakness right foot
5	I	4	None	Left hemiplegia, tuberculous hip (left)
6	I	41	Slight left hemiplegia for 1 month then right from 4th month	Slight blurring of vision, slight loss of visual field
7	I	24	Partial spinal block	Nil
8	I	21	Slight ataxia and athetosis right arm	Nil
9	I	5	Slight spasticity left foot	Nil
10	I	10	Spinal block	Nil
11	I	8	None	Mental retardation
12	A	10¹⁰/₁₂	None	Mental retardation

E, early. I, intermediate. A, advanced.

culous meningitis. The results which were obtained in the Isoniazid and Compromise Groups were satisfactory in respect both of total mortality and mortality in the first twenty-eight days of treatment. Emphasis is attached to these early deaths because it seems probable that, if the schedule of chemotherapy adopted had been ineffective, there would have been an excessive mortality in the preliminary stages of treatment. In the same way weight should be placed upon the small number of relapsed cases. Here again one would expect that, if chemotherapy were deficient, this fact would be shown up in the liability to relapse. Only 1 relapse was seen among the 68 cured patients included in the Isoniazid and Compromise Groups, a result which suggests effective cure. Finally, the return of the C.S.F. to normal was slightly more rapid in the patients receiving minimal intrathecal therapy.

We have intentionally made no attempt to apply statistical formulæ to the figures, for in such a small series containing many variable factors it would be difficult to know which statistical device to employ. But, when all the criteria of assessment point in the same direction, we believe we are justified in concluding that the reduction of intrathecal therapy is rational.

Our findings have especial importance because of the general reduction in the number of cases of tuberculous meningitis; for this means that individual units are now called on to treat few cases. Although lumbar puncture is very safe in the hands of experts, when such experience is lacking the operation can indeed be hazardous. We believe that repeated lumbar puncture with intrathecal medication need not be regarded as an essential part of the chemotherapy of tuberculous meningitis. While there is much to be said for arranging that the reduced numbers of these serious cases should be concentrated in special units, the results of this trial make treatment simpler and safer when this is not possible.

We do not want to seem to suggest the adoption of any standard pattern of treatment, for such an advocacy would be most undesirable in a disease so lethal as tuberculous meningitis. When the diagnosis is first made, cases can show great variation in their apparent severity, and in such circumstances the wise clinician is likely to attach less importance to the results of some statistically satisfactory trial and to feel that it is his duty to give the patient the benefit of every chemotherapeutic device. In such circumstances he may well feel a compelling need to administer some of the streptomycin intrathecally. Our results suggest that the duration of this period need not be long, and that the patient may thus be saved what was an undoubtedly severe discomfort. Further, as convalescence becomes established, a reduction of the number of intramuscular injections of streptomycin seems reasonable, and a course of two or three per week will prove adequate.

Summary

111 cases of tuberculous meningitis were allocated, by random selection, to three treatment groups. In the Standard Group chemotherapy was with streptomycin (by both the intramuscular and intrathecal routes) and P.A.S.; in the other two groups isoniazid was added, and the amount of intrathecal medication with streptomycin greatly reduced.

The results of the trial indicate that, when isoniazid is included in the chemotherapy, intrathecal streptomycin is not an essential part of the treatment schedule.

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HUNTING THE NEEDLE

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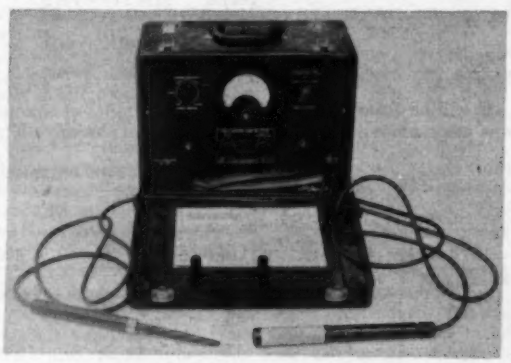
NEEDLES, or more often pieces thereof, may remain embedded in a particular site for years and cause little or no trouble; but occasionally migration takes place and sometimes symptoms call for their removal (Rogers 1942). In other cases early removal is indicated, particularly if symptoms are acute, as in the case of a stout lady who sat in a deck-chair in which there was a sewing-needle. The needle entered the buttock, and in the belief that she had been stung by a wasp a misguided friend squeezed the point of entry in an attempt to remove the sting. The needle was thereby driven more deeply into the buttock and penetrated the great sciatic nerve, from which I was called to remove it.

Broken-off pieces of needle occupying such sites as arm, hand, leg, or buttock can easily be removed if proper precautions are taken before endeavouring to find them. Yet how often, and how inadvisedly, are exploratory operations performed!

In any exploratory operation for an embedded needle, I would not only strongly advocate the use of detection apparatus such as Berman's metal-locator (see figure),



Berman's metal-locator.

but go as far as to say that without some such apparatus the surgeon should not proceed. Berman's detector consists of a galvanometer dial on which the amplitude of the oscillations indicates the approach of the seeker electrode to the metallic foreign body. After antero-posterior and lateral X-ray films have shown the position of the needle fragment, an appropriate incision is made. The point of the electrode is introduced into the wound and manipulated until maximal oscillations indicate its close approach to the foreign body; a little diligent searching there brings it to light.

The following brief reports of some cases in which it proved helpful support my contention that no attempt should be made to remove a broken-off piece of needle without its use. It not only reduces damage to tissues by limiting the extent of the exploration but also makes success assured without the dangers that accompany removal under an X-ray screen.

Case 1.—A housewife, aged 56, who had chronic sciatica, was given an injection by her doctor. The needle broke off in her right buttock. She was taken to the local hospital and told to return the next day, when she was radiographed and operated upon. The piece of needle was not found and she was reoperated upon the following day, and again exploration failed to find the needle. She was sent out with a discharging

wound and sought admission to the Cardiff Royal Infirmary. The incision was reopened, and with the help of the locator the needle readily found and removed. Proceedings were about to be taken by an irate husband against the first hospital, but were dropped by request.

Case 2.—An engineering student, given penicillin for an infected wound, was left with a broken piece of needle in his left buttock. He was transferred from a local hospital where two attempts to remove it had failed. It was easily located and removed with the help of the metal-locator.

Case 3.—A housewife was washing clothes, among which was a garment containing a sewing-needle which entered her right hand near the base of the thenar eminence and broke off. She had a constant ache in her hand which was worse when wringing out clothes. She attended a hospital casualty department, where an attempt to find the broken piece of needle failed. She was referred to the Cardiff Royal Infirmary, where the fragment of needle was easily removed with the help of the locator.

These are typical cases in which surgeons needlessly spent hours failing to find needle fragments, and in doing so unnecessarily damaging tissues, not for any want of skill but for lack of proper equipment.

COMMENTS

Except there be some very special reason, injections should be given in the outer aspect of the thigh where they can do no harm and where, should the needle fracture, pieces of it are not likely to cause symptoms.

Attempts should not be made to remove broken pieces of needle without having a metal-locator available.

The metal-locator is valuable to surgeons seeking broken pieces of needle in tissues just as the mine detector is valuable to an army advancing in a minefield.

I am much indebted to Mr. R. Ellis, of the department of radiotherapy of the United Cardiff Hospitals, who has kindly adjusted and manipulated the instrument for us whenever we have used it, and to Mr. H. Kincaid, of the surgical unit, for the accompanying photograph.

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RADIOACTIVE COLLOIDAL GOLD IN THE TREATMENT OF PLEURAL AND PERITONEAL EFFUSIONS OF MALIGNANT ORIGIN

REVIEW OF 235 CASES

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SINCE artificially produced radioactive isotopes became available many papers have appeared on the use of radioactive colloidal gold (^{198}Au) in the treatment of pleural and peritoneal effusions of malignant origin (Muller 1950, Walton and Sinclair 1952, Ireton and Ullery 1956, Chang et al. 1957, Hahn 1956). At the Royal Marsden Hospital this form of treatment was begun in 1949 (Smithers 1951), and the clinical and physical aspects of this form of irradiation were discussed by Walton and Sinclair (1952).

235 cases of malignant effusions treated at the Royal Marsden Hospital between March, 1950, and March, 1956, are reviewed here. Samples of fluid from a large number of these patients, both before and after the administration of intracavitary colloidal ^{198}Au, were studied by Prof. R. J. V. Pulvertaft, of the department of pathology, Westminster Hospital, and Prof. P. C. Koller, of the Chester Beatty Research Institute. Using a wide variety of tissue-culture techniques Professor

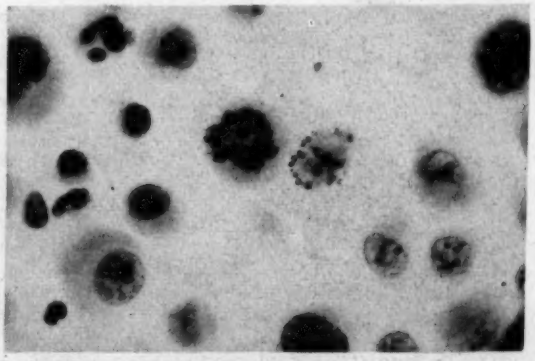

Fig. 1.—Cells in ascitic fluid: one cell in metaphase, and another loaded with aggregated particles of radioactive colloidal gold and showing degeneration (Professor Koller's preparation).

Pulvertaft has so far found it impossible to grow tumour cells found in these malignant effusions. He has kept such cells alive for four to six weeks, but has not been able to get them to multiply in vitro.

Koller (1956) has reported his observations on the cytological analysis of 98 malignant effusions. On the morphology of the cell population he classifies malignant effusions into two types: (1) effusions in which the cells occur singly or in aggregates with well-defined cell outlines (termed free-cell ascites) and (2) effusions in which the cells form masses with indistinct cell boundaries. In the second group polymorphism of chromosomes and mitotic abnormalities are commoner than in free-cell ascites. Koller finds that the cell characteristics are influenced by the volume and rate of formation of fluid and by the intervals between aspirations. After the intracavitary application of radioactive colloidal gold the total cell population and the number of dividing cells are much decreased, the range of chromosome polymorphism is greatly reduced, and colloid particles are sometimes observed within tumour cells (fig. 1), which may show eccentric chromosome fragments indicating damage caused by irradiation.

The main object of these cytological investigations was to discover cell characteristics which would indicate the likely effect of intracavitary radioactive colloidal gold on the rate of fluid formation within the cavity concerned. It is generally agreed that not more than half the patients treated derive appreciable benefit from this form of irradiation. It would therefore be most valuable if patients who would derive benefit from treatment with intracavitary colloidal ^{198}Au could be accurately selected on the cytological characteristics observed in a small sample of aspirated fluid.

At present it is, unfortunately, impossible to do this. The instillation of radioactive colloidal gold consistently reduces the number of tumour cells in an effusion for a time but often does not change the rate of formation of the fluid. Goldie and Hahn (1950) have shown that tumour cells are killed by irradiation with radioactive colloidal gold in routine therapeutic concentrations; but there is no reason to expect that the reduction in the population of free-floating cells would in any way alter the rate of formation of the fluid.

Ætiology of Effusions

The cause of the formation of fluid in malignant disease involving serous membranes is unknown; several factors may be concerned—e.g., increased transudation (secretion); diminished absorption due to obstruction of venous and/or lymphatic vessels (fig. 2); and exudation of fluid from raw neoplastic surfaces. It is most unlikely that the last factor is ever responsible for the formation

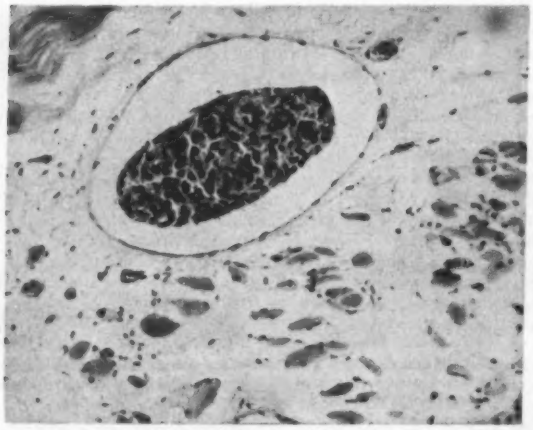

Fig. 2—Group of malignant cells (carcinoma of ovary) within an obstructed and grossly dilated lymphatic vessel in subpleural layer of diaphragm (× 195).

of any appreciable volume of fluid, because patients coming to necropsy who have had to have large quantities of fluid removed at short intervals may not show any extensive neoplastic involvement of the serous membrane in question—e.g., in Meigs's syndrome large effusions are absorbed after the removal of an ovarian fibroma which may be quite small. Conversely, an extensive involvement of a serous membrane—e.g., subpleural permeation in carcinoma of the lung or of the breast—may be accompanied either by no fluid or by only a small static pleural effusion.

In 11 of the patients under review with primary carcinoma of the breast, ovary, or cervix, or lymphosarcoma small pleural effusions were discovered in addition to the major recurring effusion in either the peritoneal cavity or the contralateral pleural sac needing treatment with radioactive colloidal gold. These small symptomless effusions, in which tumour cells were detected, either remained static or decreased over a period of some months.

It is well recognised that in some patients with malignant effusions considerable quantities of fluid may reaccumulate within a few hours of removal. Studies of the turnover of human serum-albumin labelled with radioactive iodine and of water labelled with tritium (radioactive isotope of hydrogen) have shown that about 100 litres of fluid is transferred across the vascular-peritoneal barrier in twenty-four hours (McKee et al. 1952, Prentice et al. 1952, *British Medical Journal* 1954). It is therefore readily understandable how small deviations from normal in either absorption or secretion could give rise to rapid accumulation of fluid.

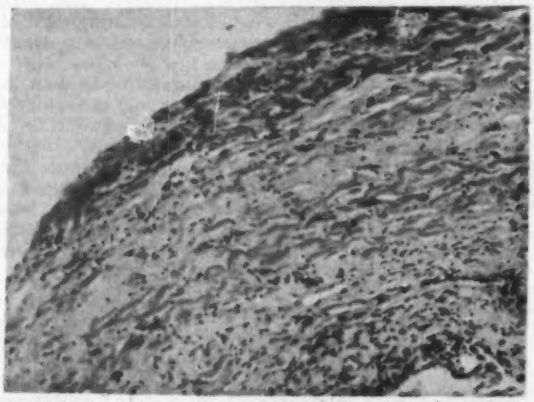

Fig. 3—Section of lung and pleura 11 weeks after intrapleural administration of 80 mC of radioactive colloidal gold, showing infiltration by malignant cells (carcinoma of breast) and thickening of pleura due to progressive organisation of fibrinous exudate (× 120).

Mode of Action of Radioactive Colloidal Gold

The following mechanisms are most likely to be involved in inhibiting the formation of fluid (Andrews et al. 1953):

(1) *The production of subendothelial fibrosis* would obliterate regional blood-vessels and lymphatics and inhibit the exudation of fluid therefrom. In some of the present patients coming to necropsy, histological examination showed thickening and fibrosis of the serous membrane previously treated with intracavitary colloidal gold (fig. 3).

(2) *The promotion of adhesions* between the visceral and parietal layers of the treated serous membrane would diminish the surface area responsible for the formation of fluid and partly obliterate the available space in which fluid could collect. At necropsy extensive adhesions are often found in the treated cavity. The formation of adhesions is, however, not essential for the success of intracavitary gold therapy: 2 patients responded well for three or four months, and then ascites again developed, and laparotomy in both cases showed that the peritoneal cavity was free from significant adhesions.

(3) *Direct Effect of Irradiation on Tumour.*—About 90% of the dose is due to beta radiation, with a half-depth value in tissue of only 0·4 mm.; the gamma radiation amounts to only a small fraction. It is therefore most improbable that these relatively small doses of irradiation produce any appreciable effect on tumour surfaces so far as the formation of fluid is concerned. In some cases of advanced mammary cancer with pleural effusions and diffuse metastases hormone therapy produces a dramatic response of the metastases in soft tissue and bones, while the pleural effusion increases owing to the retention of fluids caused by œstrogens and androgens. In these cases it can reasonably be assumed that the pleural metastases are responding in a similar dramatic fashion as the other secondary deposits, but that the pleural fluid increases because it is not being secreted by the tumour. Furthermore Bonte et al. (1956) report that the intrapleural administration of nitrogen mustard in cases of recurrent malignant effusions secondary to breast cancer gives results similar to those achieved by treatment with colloidal gold. Except for non-specific general radiomimetic effects, nitrogen mustard does not possess any selective action on breast cancer; hence any benefit produced by this therapy is more likely to be due to the production of fibrosis than to any selective effect on malignant cells.

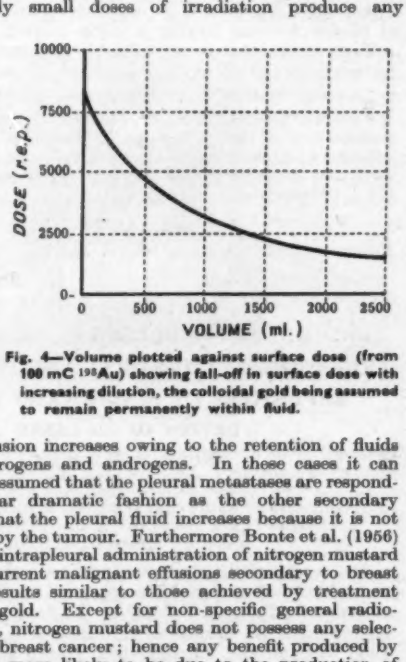

Fig. 4—Volume plotted against surface dose (from 100 mC ^{198}Au) showing fall-off in surface dose with increasing dilution, the colloidal gold being assumed to remain permanently within fluid.

Technique of Administration of Intracavitary Colloidal Gold

Every effort is made to remove all available fluid before the intracavitary instillation of radioactive colloidal gold, because fluid in the treated cavity will reduce the dose-rate to the serous membrane, if the gold particles remain within the cavity. Fig. 4 illustrates the effects of dilution on the surface dose delivered by 100 mC of colloidal ^{198}Au. In practice, however, it is well known that particles of colloidal gold are fairly rapidly removed from the intracavitary fluid and deposited in aggregates of various sizes in the subendothelial con-

nective tissue. Hahn (1956) has suggested that a considerable volume of saline solution should be given simultaneously with the colloidal gold because this procedure would accelerate the deposition of gold in the subendothelial tissues.

Patients presenting with large pleural effusions should have the greater part of the fluid aspirated one or two days before the start of treatment with colloidal gold; if this step is omitted, it will only be possible, at the time of instillation of the colloid, to aspirate three to four pints of fluid before distress, due to mediastinal shift, causes further attempts to remove the remaining fluid to be discontinued.

In some patients with extensive infiltration of the visceral pleura associated with pulmonary collapse the removal of two or three pints of fluid produces a considerable negative intrapleural pressure, which causes such severe pain that further aspiration has to be abandoned.

Peritoneal effusions are best aspirated with a long (15 cm.) cannula having one or two side-openings. By puncturing the peritoneum in the para-umbilical region it is possible to explore most parts of the peritoneal cavity. Where severe symptoms require urgent removal of fluid a polyethylene tube is introduced into the peritoneal cavity, through the cannula before its withdrawal, and colloidal ^{198}Au can then be instilled through this tube at any convenient time.

After the administration of intracavitary colloidal gold the patient is nursed in a special tipping bed. Counting over the peritoneal or the pleural cavity is done routinely, and when this shows any regions of abnormally high or low activity an attempt is made to obtain more uniform distribution by postural tipping. In only 2 cases was it considered necessary to remove the colloidal ^{198}Au due to local excessive activity; in both patients (one pleural and one peritoneal) about half the administered dose was recovered about twenty-four hours after instillation, and no evidence of any high-dose effects was observed.

Contra-indications

If a reasonable proportion of the fluid estimated clinically and radiographically cannot be aspirated, and if the patient's general condition is very poor and deteriorating, the administration of radioactive gold causes considerable distress and general systemic upset, thereby accelerating and making more unpleasant the terminal phase of the disease without any prospect of affording relief.

TABLE I—EFFUSIONS IN 235 PATIENTS. RESPONSE TO INTRACAVITARY COLLOIDAL GOLD

Primary site of neoplasm	No. of cases	No. of effusions	Good inhibition of formation of fluid	Some inhibition of formation of fluid	No effect	Unknown	Rejected
Breast ..	76	61 Pleural	15	10	9	26	1
		15 Peritoneal	5	1	1	..	..
Ovary ..	71	3 Pleural	1	..	1	1	..
		68 Peritoneal	8	..	5	31	24 (Prophylactic)
Lung ..	19	19 Pleural	4	4	4	5	2
Unverified	18	2 Pleural	1	..	..	1	..
		16 Peritoneal	6	..	1	9	..
Reticuloses	15	12 Pleural	7	1	3	1	..
		3 Peritoneal	3	..	..	..	..
Colon ..	11	11 Peritoneal	2	..	1	4	4 (Prophylactic)
Miscellaneous *	8	3 Pleural	..	..	1	..	2
		5 Peritoneal	4	..	..	1	..
Uterus body	8	2 Pleural	1	..	1	..	..
		6 Peritoneal	1	..	2	2	1
Stomach ..	7	7 Peritoneal	..	..	..	7	..
Uterus cervix	2	1 Pleural	..	..	1	..	..
		1 Peritoneal	1	..	..	..	..
Total ..	235		59	16	30	96	34

* Portal cirrhosis, 3; primary adenocarcinoma of Liver, 1; cancer of gall-bladder, 1; cancer of pharynx, 1; cancer of lacrimal gland, 1; cancer of urinary bladder, 1.

TABLE II—26 PATIENTS WHO SURVIVED A YEAR OR LONGER

Site of primary neoplasm	No. cases	Survival (yr.)				
		1	2	3	4	6
Breast	10	4	1	1	2	2
Ovary	8	6	2	..	..	..
Lymphosarcoma (Hodgkin's disease)	3	..	3	..	..	..
Rectum	1	..	..	1	..	..
Lung	2	2	..	..	..	..
Cervix	1	1	..	..	..	..
Unknown	1	1	..	..	..	..

Assessment of Results

Table I shows the effect produced by intracavitary colloidal ^{198}Au on the formation of fluid, and the distribution of cases according to the site of the primary neoplasm and the serous cavity involved. As would be expected, the breast and ovary are the organs most affected. The results are classified as follows:

(1) *Good Inhibition of Formation of Fluid.*—In this group are included patients who, before treatment, required numerous aspirations of large quantities of fluid at short intervals. After the instillation of radioactive colloidal gold the further formation of fluid was completely arrested, or only one or two aspirations were required over a period of many months. In this category are 26 patients who survived longer than a year (table II).

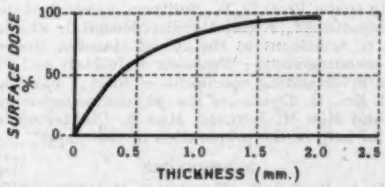

Fig. 5—Thickness of fluid layer of colloidal gold plotted against surface dose.

(2) *Some Inhibition of Formation of Fluid.*—Under this heading are classified patients in whom the rate of accumulation of fluid was retarded; after treatment the fluid was aspirated at longer intervals.

(3) *No Effect.*—In these patients the amounts of fluid and the frequency of aspiration showed no appreciable change after treatment.

(4) *Unknown.*—In this group are included patients dying within four weeks of treatment; patients who had required only one or two aspirations before treatment and were apparently not forming fluid rapidly or in appreciable quantity; and cases in which no follow-up details were obtained about aspirations.

(5) *Rejected.*—In this category are grouped patients given only a small and inadequate dose of radioactive gold because of loculation of fluid or rapidly deteriorating general condition; and patients given prophylactic treatment after laparotomy when an ovarian cyst ruptured during removal or peritoneal seedling deposits, with or without free fluid, were discovered. On these grounds twenty-four patients with ovarian carcinoma were given "prophylactic" gold therapy. Because of wide differences in the stage of the disease, the histology of the lesion, and other forms of additional treatment afforded—e.g., supplementary irradiation with X rays or with radium—it was impossible to assess the value of treatment with radioactive colloidal gold in this group of patients; furthermore, the natural history of malignant disease of the ovary is extremely variable.

The term "seedling deposits" has been used by many surgeons and gynæcologists to include metastatic lesions as large as 2 cm. in diameter. Even in the absence of adhesions it is impossible to irradiate uniformly every aspect of the peritoneal membrane with radioactive colloidal gold, because a layer of colloid 2 mm. thick (fig. 5) is required to surround

every surface of the membrane, and, in spite of postural tipping, coils of gut lie closely apposed to each other and to the adjacent parietal peritoneum without any intervening layer of fluid. On these grounds it is suggested that uniform irradiation of the peritoneal cavity is best delivered by external means, and that intracavitary gold therapy should only be used as a valuable supplementary form of irradiation which, because of its very superficial action and small integral dose, does not appreciably lower the general systemic tolerance or make it necessary to decrease the dosage delivered by external irradiation.

Conclusion

The administration of intracavitary radioactive colloidal gold is very often the only possible form of treatment that can be given to the unfortunate patient with a rapidly recurring effusion of malignant ætiology necessitating repeated aspirations at short intervals. The results of this therapy are by no means dramatic, but a gratifying proportion of patients obtain appreciable benefit in that the formation of fluid is inhibited.

Summary

The results of treating 235 cases of pleural and peritoneal effusions of malignant origin with radioactive colloidal gold are analysed.

The cause of the formation of fluid secondary to malignant disease is still unknown; so is the mode of action of intracavitary radioactive colloidal gold in inhibiting the formation of that fluid.

The technique of this treatment and its contra-indications are described.

I wish to thank Prof. D. W. Smithers, director of the radiotherapy department, Royal Marsden Hospital, who initiated this form of treatment at the Royal Marsden Hospital, for help and encouragement; Professor Pulvertaft and Professor Koller for investigating specimens of fluid; and Dr. N. G. Trott and Mrs. G. Dyche, of the physics department of the hospital, and Miss M. Johnson, Miss K. Chatterton, and Mr. J. Gibbs for help in the preparation of this paper.

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RECURRENT ABNORMALITIES OF THE THIRD STAGE OF LABOUR

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THE risk of loss of life or damage to health from bleeding during pregnancy and labour is still serious. Hæmorrhage still ranks second only to toxæmia of pregnancy as a cause of maternal mortality, and may rank first as a cause of maternal morbidity. The commonest cause of such dangerous bleeding has for many years been third-stage hæmorrhage—a complication which is particularly hazardous and alarming when it happens in a patient's home. This is, moreover, a constant threat which no amount of antenatal care can directly prevent. Good antenatal care can of course influence postpartum hæmorrhage by ensuring that the patient is in as good a general condition as possible to withstand hæmorrhage, and by the selection for hospital confinement of patients in whom the risk of postpartum hæmorrhage is increased.

It is our purpose to draw attention to a type of patient running this greater risk. When a patient has previously had a third-stage hæmorrhage, the risk of hæmorrhage in a subsequent labour is materially increased. This is already known by many, but its importance is not yet appreciated by others. Many standard textbooks make no reference to it, and some mention it only briefly. Roques (1955) and Donald (1955) recommend that a patient with a history of postpartum hæmorrhage should be confined in hospital; Johnstone and Morris (1955) recommend hospital confinement after two previous abnormalities. The extent of increased risk, and how far it is influenced by the number of previous abnormalities or by intervening normal pregnancies, are nowhere referred to, so we have studied these questions further.

Cases Studied

We have investigated the outcome of the third stage of labour of all women giving a history of a previous third-stage abnormality who were delivered in the university unit at the Jessop Hospital for Women and in the City General Hospital, Sheffield, since 1952. 105 such women were seen in 132 pregnancies and labours. In each case attention was drawn on her notes to the previous third-stage hæmorrhage, and a doctor was present at every delivery in an attempt to minimise the risk of recurrence and to reduce the blood-loss. Only when the delivery was normal was the case included in the series; 6 labours where this was not so have, therefore, not been included in the total of 132. In 101 patients the original abnormality had been postpartum hæmorrhage—without manual removal of the placenta in 54 and with manual removal in 47—and in 4 the original abnormality had been a secondary postpartum hæmorrhage.

Results

These cases have been divided into three groups, according to the outcome of the third stage of labour:

Group 1.—The third stage was entirely normal, the placenta separating without difficulty and being expelled by the patient or by the attendant, with small blood-loss.

Group 2.—The third stage was definitely abnormal—either there was a postpartum hæmorrhage of more than 20 oz. (with or without manual removal of the placenta), or manual removal of the placenta was required for bleeding, though the total loss did not amount to more than 20 oz.

Group 3.—The third stage was potentially abnormal—either because bleeding caused concern before complete separation of the placenta, requiring placental expression of the Crédé type and intravenous ergometrine; or, in a small number of cases, because bleeding was brisk after expulsion of the placenta, again requiring control by the use of an oxytocic drug and fundal massage. In these cases the blood-loss did not amount to more than 20 oz. The cases in this group are separated because they are an indication of how often prompt treatment is required in this type of case to prevent further bleeding. When we consider the precautions taken in the series to prevent blood-loss, there can be little doubt that under less favourable circumstances, such as a delivery in the home with the doctor unable to be present, many of these cases would have fallen into group 2.

In the 132 pregnancies the third stage was normal in 73 women (55%). In 30 (23%) it was abnormal; 21 patients lost more than 20 oz. of blood, 9 requiring manual removal, and 9 (7%) required manual removal of the placenta for bleeding which did not amount to more than 20 oz. In 29 women (22%) there was potential abnormality as defined above. Thus in 59 cases (45%) complications arose requiring treatment during the third stage of labour; in about half of these abnormal bleeding was prevented and in half it was not.

The results were related to the number of previous abnormalities (table I). Where a previous third stage was potentially abnormal (group 3), this has not been included

as a previous abnormality; we have accepted only those abnormal by definition (group 2).

After one abnormality, 59 in 100 third stages of labour were normal, 20 abnormal, and 21 potentially abnormal. After two previous abnormalities, of the total of 25 third stages, 11 were normal, 7 abnormal, and 7 potentially abnormal. After three such abnormalities, of 6 third stages 3 were definitely abnormal, 1 potentially abnormal, and 2 normal. 1 woman, who had had 4 previous abnormalities, had a normal third stage.

TABLE I—RESULTS RELATED TO NUMBER OF PREVIOUS ABNORMALITIES

—	No. of previous abnormalities			
	1	2	3	4
Total pregnancies	100	25	6	1
Results:				
Normal third stage	59	11	2	1
Postpartum haemorrhage	13	5	3	—
Other manual removal	7	2	—	—
Potential abnormality	21	7	1	—

Thus, while there was a recurrence in a fifth of the labours following one abnormality, there was a recurrence in a third after more than one.

Effects of an Intervening Normal Pregnancy

It seemed possible that, if an abnormality was followed by a pregnancy with a normal third stage, this might be an indication that the risk of subsequent recurrence was small, and that the precautions could therefore be relaxed. Of 14 such cases, in 9 the third stage was normal, in 3 it was abnormal, and in 2 a developing abnormality was successfully treated. This figure—a fifth of the patients having a recurrence—is comparable with a similar proportion for all patients following one abnormality (table II), and suggests that the tendency to abnormality persists, and vigilance should not be relaxed.

This can be seen in another way. If we consider the proportion of patients who remained free from a recurrence following the original abnormality, we find it falling markedly with each successive pregnancy (table II). After one further pregnancy 69 of the 105 women were free from recurrence; after two further pregnancies

TABLE II—NUMBERS OF PATIENTS WITH AND WITHOUT RECURRENCE AFTER SEVERAL FURTHER PREGNANCIES

—	Total	Recurrence	Non-recurrence
After 1 further pregnancy	105	36	69
After 2 further pregnancies	40	21	19
After 3 further pregnancies	24	17	7

19 of 40 women were free (18 having had one recurrence, and 3 having had two recurrences); after three further pregnancies only 7 of 24 patients were free from a recurrence (13 women having had one, 3 having had two, and 1 having had three recurrences).

Effect of Prophylactic Treatment

Although a doctor was present at delivery in every case, no hard-and-fast rules were laid down for management of the third stage; some chose to conduct the third stage in the usual manner, and others preferred to give intravenous ergometrine (0·5 mg.) with delivery of the anterior shoulder. Consequently, the women who received prophylactic intravenous ergometrine can be compared with those who did not (table III).

63 women received prophylactic intravenous ergometrine with the anterior shoulder; 47 had a normal third stage (using the word here in the sense of completely uncomplicated), 11 had a postpartum haemorrhage or manual removal, and 5 had a potential abnormality. Of the 69 patients who received no prophylaxis, only 26 had a normal third stage; in 19 it was definitely abnormal, and in 24 potentially so.

TABLE III—EFFECT OF PROPHYLACTIC ERGOMETRINE

—	Prophylactic intravenous ergometrine	No prophylaxis
Total	63	69
Result:		
Normal third stage	47	26
Postpartum haemorrhage	5	16
Other manual removal	6	3
Potential abnormality	5	24

Though it seemed from these figures that the number of women requiring treatment for a developing abnormality was much greater in the group not receiving prophylaxis, it was possible that this might be partly explained if this group contained a higher proportion of serious cases after more than one abnormality. But in fact in all three groups (table IV) the proportion of abnormality and potential abnormality is higher in those who did not receive prophylactic treatment; moreover, so far from this group containing the greater number of women who had had more than one previous abnormality, the opposite is the case. The apparent benefit of prophylactic ergometrine therapy is, therefore, a real one. Nonetheless,

TABLE IV—RELATIONSHIP OF TREATMENT TO NUMBERS OF PREVIOUS ABNORMALITIES

—	No. of previous abnormalities					
	1		2		3	
	Prophylaxis	No prophylaxis	Prophylaxis	No prophylaxis	Prophylaxis	No prophylaxis
Total	42	58	16	9	4	2
Result:						
Normal third stage	35	24	9	2	2	..
Postpartum haemorrhage	1	12	2	3	2	1
Other manual removal	4	3	2	..	..	..
Potential abnormality	2	19	3	4	..	1

although this form of prophylactic treatment will prevent a number of cases of recurrent third-stage haemorrhage, it will not prevent all, and serious blood-loss of more than two pints was still seen on a few occasions even after this treatment.

Original Abnormality Related to Recurrence

In 54 patients (table V) the original abnormality was postpartum haemorrhage without manual removal. 30 of these women had suffered no recurrence, while 24 women had 34 pregnancies complicated by further abnormality; in 25 of these the recurrence was of a similar nature, but in 9 manual removal was needed. In 47 women in whom manual removal of the placenta had been performed originally 29 remained free from recurrence, while 18 were again abnormal in 22 pregnancies. Manual removal

TABLE V—NATURE OF ORIGINAL ABNORMALITY AND NATURE OF RECURRENCE

Original abnormality	Total	Non-recurrent	Recurrent	Nature of recurrence		
				Postpartum haemorrhage only	Manual removal	Secondary postpartum haemorrhage
Postpartum haemorrhage	54*	30	24 (34 pregnancies)	25	9	—
Manual removal	47	29	18 (22 pregnancies)	4	18	1
Secondary postpartum haemorrhage	6*	4	2	1	1	—

*2 patients had both a primary and a secondary postpartum haemorrhage originally.

was repeated in 18 of these and avoided in only 4. 1 woman, who required manual removal for a recurrence, had a second postpartum hæmorrhage some days later, and an adherent cotyledon was removed by curettage. In these two groups, therefore, in about three-quarters of the cases the type of recurrence was similar to that of the original abnormality.

6 women originally suffered secondary postpartum hæmorrhage; this was the only abnormality in 4, but in 2 it followed primary postpartum hæmorrhage some days previously. 1 of these 2 had a recurrence of postpartum hæmorrhage subsequently, while 1 of the 4, with only secondary postpartum hæmorrhage, required manual removal of the placenta in her next pregnancy.

Effect of Possible Non-recurrent Factors

It seems possible that in certain cases the original abnormal third stage might have been largely due to factors operating in that pregnancy only; these women would therefore not run the same risk of recurrence. There were 10 such women in this series; 5 had had an operative delivery under general anæsthesia, 4 a previous antepartum hæmorrhage, and 1 a twin pregnancy. Subsequently, these patients had a total of 17 pregnancies without recurrence of the third-stage fault.

In view of the many difficulties involved, no attempt has been made to determine what part mismanagement may have played either in the original abnormality or in a recurrence.

Patients Treated by the Flying Squad During the Period of the Survey

Lastly we should like to give the results of another group of patients treated by the hospital staff during the period of this survey, but not included in it, to give an indication of the size of the problem presented by the type of case we are discussing and to draw attention to the need for more widespread appreciation of its severity. These are the patients for whom the services of the emergency unit (flying squad) were requested.

During this period 106 patients were treated by the flying squads from the two hospitals concerned. 26 had previously had an abnormal third stage of labour, and no less than 20 of the 26 lost over 2 pints of blood. This may be compared with only 9 women losing more than 2 pints of blood in the 132 labours in the series conducted in hospital, and is again a reminder of what might happen to those women considered potentially abnormal in this series if labour had been conducted under less favourable conditions.

Discussion

These results clearly show the increased incidence of third-stage complications in patients with a previous abnormality. Nearly a quarter of all the pregnancies reviewed here were complicated by postpartum hæmorrhage or manual removal of the placenta or both—a rate between four and five times as high as that for all deliveries in the two hospitals concerned during the period of the survey. After a previous abnormality a fifth of the pregnancies were complicated by recurrence, and the evidence here suggests that this risk is not materially different subsequently, if a normal third stage follows in the next pregnancy after the abnormality; precautions should not be relaxed in this type of case. There is, moreover, a trend to an even greater proportion of abnormalities in pregnancies after two or three previous abnormalities than after one only (table I), and it was these mothers who caused us the greatest concern. The figures of a recurrent abnormality in more than a quarter of the pregnancies after two previous faults, and in half the patients after three, indicate this trend, but they do not indicate the severity of the third-stage bleeding in some of these cases. Despite our efforts to prevent it, hæmorrhage was alarming on several occasions. An example of the formidable nature of the bleeding in this type of case is given in the following record.

Case 1.—A woman had her first 5 babies without recorded abnormality of the third stage. Her 6th, 8th, and 9th babies were born normally, but in each case the third stage was complicated by a retained placenta and postpartum hæmorrhage, and she required manual removal and a blood-transfusion. At her 10th confinement every effort was made to prevent a recurrence. One of us (W. A. W. D.) was present at the delivery, and an anæsthetist was standing by, our intention being to carry out manual removal at once if prophylaxis failed. Although ergometrine 0·5 mg. was given with the delivery of the anterior shoulder, bleeding began before any resulting contraction was detected; and it was not controlled, neither was the placenta expelled, following the contraction. Anæsthesia was at once induced, but bleeding continued despite control of the fundus. The placenta was removed with ease as quickly as possible, but hæmorrhage continued throughout the operation, and bimanual compression was necessary for a short time before the bleeding stopped. In all, almost 5 pints of blood was lost, this quantity of blood being returned to the patient by transfusion.

Many of these women with several previous abnormalities are of high parity, and so fall into the group in which the risk of hæmorrhage is already great, and hæmorrhage especially serious (Dewhurst 1952).

Although an attempt was made in each case to confirm the previous abnormality, either by reference to our own or to other hospital records, or to the patient's doctor, it was not always possible to get this confirmation. The few cases where proof of the original fault was lacking, however, were characterised not by the difficulties which arose in the labours in which we were concerned, but rather by the ease with which the third stage was managed when serious trouble was anticipated.

One notable case was the only patient who presented with a history of four previous abnormalities; confirmation could be obtained of only two of these, both the other confinements having taken place in the patient's home before the arrival of a midwife or doctor; and though postpartum hæmorrhage may well have occurred, as the patient maintained, it might also have been prevented if a medical attendant had been there. To exclude these few cases, however, would not reduce the incidence of the complications recorded here, but would increase it.

In the management of these cases the use of intravenous ergometrine with the delivery of the anterior shoulder results in fewer abnormalities and potential abnormalities than when no prophylaxis is used. This is most evident when the results after one previous abnormality are examined (table IV). The rate of postpartum hæmorrhage and manual removal taken together in the non-prophylactic group is more than twice that in the prophylactic group. The number of cases where a developing abnormality responded to treatment is even more strikingly different in the two groups, the group of women receiving no prophylaxis having nearly five times as many cases as the other. Only the rate of manual removal with less than 20 oz. blood-loss is higher in the patients receiving intravenous ergometrine—an observation made elsewhere by others studying the value of this form of treatment (Snaith 1951, Martin and Dumoulin 1953, Vartan 1953). It seems that in some cases postpartum hæmorrhage is prevented only at the expense of manual removal—not too big a price to pay for preventing excessive blood-loss.

One small pitfall arising from the successful use of prophylactic ergometrine must be mentioned. We have already shown that the risk of recurrence was not materially reduced if a normal third stage of labour had followed a previous abnormality. This is even more important to emphasise if the uncomplicated third stage has followed the use of intravenous ergometrine. Postpartum hæmorrhage might have followed without this treatment, and its success should not be considered any safeguard against subsequent abnormality. The following case illustrates this point well.

Case 2.—A woman required manual removal of the placenta and a blood-transfusion at her first confinement.

With her second confinement she was admitted to hospital, and the third stage was conducted by giving her ergometrine intravenously as the anterior shoulder was being delivered. The placenta separated easily and blood-loss was small. When she became pregnant the third time she attended the same hospital, but was told that, as there had been no complications after the birth of her second child, there was no need for her to be confined in hospital. She was, therefore, delivered at home, and, though the baby was born normally, soon afterwards there was profuse hæmorrhage with the placenta still *in situ*. On arrival of the flying squad, she was found to be very shocked, the measured blood-loss at that time being 4 pints. She was treated by blood-transfusion and Crédé's expression of the placenta, and ultimately made a good recovery.

The only class of patient in whom it seems at all likely that the risk of recurrence is less striking than usual is that in which the original abnormality was largely due to factors, such as antepartum hæmorrhage or delivery under general anæsthesia, operating only at the time of the previous abnormality. Further evidence is desirable, however, on this point, before recommending any relaxation of precautions in subsequent confinements.

Recurrences followed both the commoner forms of third-stage abnormality (table v), and in each the type of recurrence resembled the type of the original abnormality in the majority of cases. It seems likely that a similar risk attends secondary postpartum hæmorrhage, but as these cases were so few no more definite view can be formed.

It is clear from what has been shown here that women who have previously had a third-stage abnormality should not be confined at home if this can be avoided. That they are still confined at home is shown by the fact that a quarter of the flying-squad cases treated during this period were made up of such patients.

In some of the flying-squad cases the reason for home confinement was that the practitioner was unaware that any special risk was run by this type of patient. In others he had not been informed by the patient (sometimes she did not know herself), or by his colleagues in hospital, of the previous hæmorrhage. Occasionally a normal third stage in the next pregnancy had lulled the attendants into a false sense of security (case 2). To try to reduce the numbers of these patients requiring treatment outside hospital, it seems advisable to recommend that, following an abnormal third stage of labour in hospital, both the patient and her doctor should be informed of the complication which arose, and the patient be advised to seek hospital confinement subsequently. Similarly the practitioner should pass on to the hospital accurate information of the third-stage difficulties if they were originally met with at home. Should she refuse to go to hospital, or for some other reason be confined at home, intravenous ergometrine should be given with delivery of the anterior shoulder.

Summary and Conclusions

105 women with a history of postpartum hæmorrhage, manual removal of the placenta, or secondary postpartum hæmorrhage were treated in 132 pregnancies and labours in the university unit of the Jessop Hospital for Women and the City General Hospital, Sheffield. In almost a quarter of all the labours an abnormality of the third stage of labour recurred, and in the same proportion of cases a developing abnormality was successfully dealt with by prompt treatment. After two or three previous third-stage faults, the rate of recurrence was higher than after one only. Bleeding tended to be most dangerous and severe in the woman who had had many children and who had had several previous abnormalities. No evidence was found to suggest that the risk of recurrence was smaller if a normal third stage of labour had followed the original abnormality.

In just over half the patients the third stage of labour was conducted along the usual lines; the remainder received prophylactic intravenous ergometrine with delivery of the anterior shoulder. In the prophylactic group a lower rate of abnormality and potential abnormality was recorded, despite the fact that this group contained a disproportionate number of patients with more than one previous abnormality. Even with prophylaxis, however, there was serious bleeding on several occasions.

Both postpartum hæmorrhage and manual removal of the placenta were followed by an increased risk of recurrence, in the majority of instances the recurrence being similar in nature to the original abnormality; the risk of recurrence seemed similar after a secondary postpartum hæmorrhage, though too few cases were observed for a more definite view to be formed.

There is some evidence that if the original abnormality had been largely due to temporary causes, such as antepartum hæmorrhage or delivery under general anæsthesia, the risk of recurrence in this type of case might be smaller than that in the series as a whole.

Attention has been drawn to those cases in which third-stage bleeding began before complete separation of the placenta, or caused concern immediately after placental delivery, though the total loss of blood did not exceed one pint. It is suggested that under less favourable circumstances a number of these developing abnormalities would have become postpartum hæmorrhage by definition. Evidence to support this view is given by the fact that, though in the series of 132 labours conducted in hospital only 9 women lost more than 2 pints of blood, during the same period the flying-squad treated 26 patients with recurrent third-stage abnormality, 20 of whom lost more than this amount.

These 26 patients, who had previously had an abnormal third stage of labour and who required flying-squad treatment, show, moreover, that some of these women in potential danger are still being confined at home. We consider that hospital confinement should be sought for all women who have had a previous third-stage abnormality, and that, if delivery at home cannot be avoided, prophylactic intravenous ergometrine, given with the delivery of the anterior shoulder, provides the surest means of preventing a recurrence.

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EXPECTORANTS AND SPUTUM VISCOSITY

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THE efficacy of expectorant drugs has always been a matter of controversy. Those who believe that they work have had to rely largely on the results of animal or in-vitro experiments for support, or on the traditions of clinical practice, for objective trials in human beings have been very few—probably because they are not easy to carry out. Alstead (1939) found that several popular expectorants, such as potassium iodide and ipecacuanha, when given in normal dosage failed to increase the sputum output of chronic bronchitics; but his work has been criticised on the ground that sputum volume is influenced by many factors and is therefore an unreliable index of expectorant efficiency. Sputum viscosity would seem likely to be a more exact yardstick. There have been

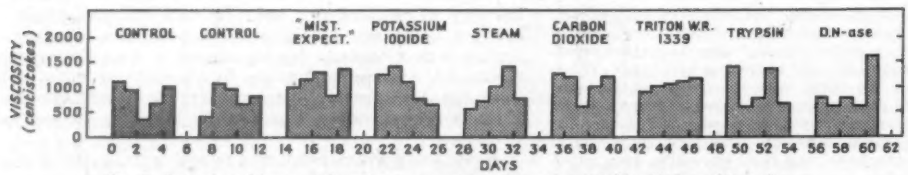

Fig. 1—Response of sputum viscosity to expectorants: man, aged 27, with bronchiectasis.

several reports of in-vitro experiments to measure the effect of expectorant drugs on the viscosity of sputum, but the only serious attempt to test their efficacy in patients seems to be that of Basch et al. (1941). Their conclusions have been widely quoted as evidence that expectorants do lower sputum viscosity in vivo, but close study leads to doubt as to whether many of the conclusions are in fact justified by the experimental evidence.

It has therefore been thought worth while to repeat the work of Basch et al., and to test the effect of both classical expectorant drugs and some of the more recent enzyme preparations on the viscosity of sputum in vivo.

Materials and Method

Suitable patients were not easy to come by. They had to be suffering from a chronic chest disease which was more or less static, so that the quantity and quality of their sputum would be unlikely to change during the weeks of testing. For technical reasons the output of sputum had to be fairly large and reasonably viscid. Moreover, only patients who were not receiving treatment likely to affect sputum output could be chosen. It was felt that out-patients could not be observed closely enough to ensure the absence of extraneous influences, so only hospital inpatients were tested. Finally, the patients had to be fit enough for the experiments and willing to cooperate in them.

Altogether 9 patients (8 men, 1 woman) were tested, though not all received the full range of expectorants. 7 had chronic pulmonary tuberculosis and 2 chronic bronchiectasis.

In every case the whole sputum expectorated during each twenty-four hours was collected, its volume measured, and viscosity of the total specimen determined. One or two five-day control periods on no treatment enabled a base-line to be established; then the following treatments were given consecutively, each for a period of five days, with two days' rest after each treatment:

1. Oral mist. ammon. et ipecac. *N.F.*
2. Oral potassium iodide.
3. Inhalation of steam.
4. Inhalation of 5% carbon dioxide and 95% oxygen.
5. Inhalation of aerosol 'Triton W.R.1339'.
6. Inhalation of aerosol trypsin.
7. Inhalation of aerosol deoxyribonuclease.

Viscometry

The method adopted by Basch et al., which essentially consisted in measuring the rate of sputum-flow through a narrow glass tube, proved in our hands to be unsatisfactory, in that consistent readings on the same specimen could not be obtained. We therefore used a Universal Torsion Viscometer (Gallenkamp), which measures the viscosity of a fluid sample by its damping effect on the rotation of a metal cylinder suspended in it by means of a torsion wire.

A standard torque of one cylinder-revolution is first applied to the wire. On its release the cylinder rotates freely one complete revolution, then a further amount which is proportional to the viscosity of the surrounding fluid. A dial is attached to the cylinder, and the viscosity can be read in degrees from 0° to 360°. A calibration-chart enables these readings to be converted to Redwood seconds, and for convenience of graphic representation these can be further converted to centistokes by means of a nomogram. The method is similar to that used by Palmer (1957).

We found that this instrument gave consistent readings, but had the drawback that measurements could be made only on volumes of sputum greater than 50 ml. We therefore used, instead of the metal cup supplied, a 'Perspex' cup 32 mm. in diameter and 50 mm. in height, which enabled us to use 25 ml. of sputum.

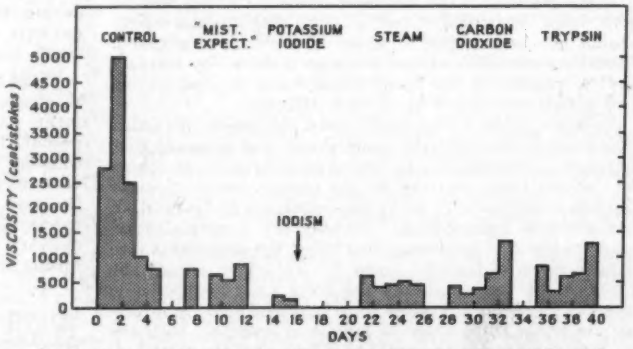

Fig. 3—Response of sputum viscosity to expectorants: man, aged 54, with pulmonary tuberculosis.

The suspension-wires used were either 36 or 30 s.w.g. (0·2 or 0·3 mm.) in diameter, and the cylinder was 17·4 mm. in diameter.

Since some of the sputum specimens were potentially infective, the whole apparatus was enclosed in a perspex shield with apertures for manipulation. This had the dual advantage of protecting the operator and of ensuring freedom from air-currents and changes in temperature, which might affect readings.

Only fairly viscid specimens could be measured accurately, and several patients had to be rejected because their sputum was too thin and mucoid. This was hardly a disadvantage, however, for the value of expectorants must surely depend largely on their ability to deal with thick mucopurulent secretions.

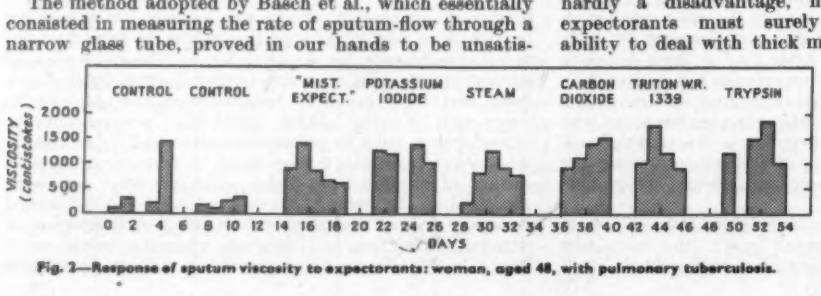

Fig. 2—Response of sputum viscosity to expectorants: woman, aged 48, with pulmonary tuberculosis.

Results

Control Periods

During these periods sputum viscosity in most patients remained fairly constant, but occasionally large variations were independent of sputum volume.

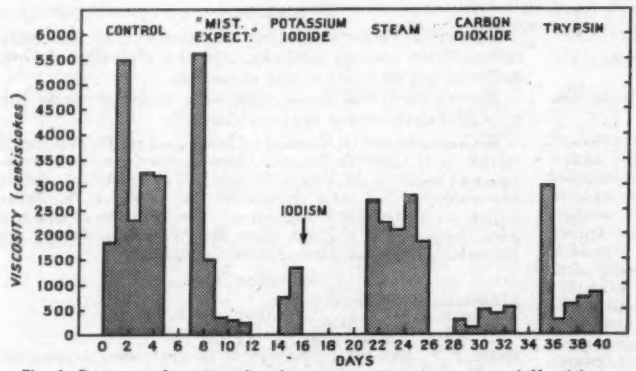

Fig. 4—Response of sputum viscosity to expectorants: man, aged 61, with pulmonary tuberculosis.

Mist. Ammon. et Ipecac. N.F.

This classical " mist. expect." was given by mouth three times daily in doses of ½ fl. oz. (15 ml.).

In 2 patients sputum viscosity was lowered ; in 3 it was increased ; in 4 it was unaltered.

Potassium Iodide

The consensus of opinion on this traditional expectorant seems to be that the usual pharmacopœial dose of gr. 3 (0·2 g.) has little or no clinical effect ; but Herxheimer and McAllen (1952), among others, have claimed that doses of gr. 15–25 (1–1·6 g.) are effective, and that they can be tolerated by most patients. 7 of our patients, therefore, received increasing oral doses of potassium iodide, made up in a mixture with liq. extr. liquoricæ and chloroform water ; gr. 5 (0·3 g.) doses were given three times on the first day, gr. 10 (0·6 g.) doses on the second day, and gr. 15 (1 g.) doses on the third and subsequent days.

In 2 patients sputum viscosity was lowered, and in 1 of these the effect was very striking (fig. 3). In 1 patient it was increased. In 4 it was unaltered. In the 2 patients in whom the sputum viscosity was diminished, symptoms of iodism developed on the gr. 10 (0·6 g.) doses, and in their cases, therefore, the drug was discontinued after two days. They might have become accustomed to it, but in the circumstances it was felt that it was unwise to persevere with a drug that was causing distress. None of the other patients, whose sputum viscosity was not lowered, had symptoms of iodism. It seems possible, therefore, that to lower sputum viscosity effectively with potassium iodide it is necessary to produce iodism.

Steam

This was given by means of a Nelson inhaler for fifteen minutes three times each day.

9 patients received this treatment. In 1 patient sputum viscosity was lowered ; in 3 it was increased ; in 5 it was unaltered.

Carbon Dioxide

Banyai (1934, 1952) claims that inhalations of 5% carbon dioxide with 95% oxygen " stimulate respiration . . . lead to forceful peristaltic movements of the bronchi . . . liquefy mucopurulent inflammatory exudate that stagnates in the bronchial tract." He is supported by Herxheimer and McAllen (1952).

Such inhalations were given to 8 patients through a plastic face-mask for fifteen minutes three times daily. In 2 patients sputum viscosity was lowered ; in 1 it was increased ; in 5 it was unaltered.

Triton W.R. 1339

This is a detergent or " wetting agent " and is the chief constituent of 'Alevaire,' a proprietary solution which on nebulisation produces so-called " cold steam." We used a 0·5% solution of 'Triton W.R. 1339' in distilled water, as 'Alevaire' itself contains other substances which might conceivably affect sputum viscosity, and we wished to measure the effect of a detergent pure and simple. A number of claims have been made for the expectorant efficiency of " cold steam " (Miller and Boyer 1952, Ravenel 1953). Palmer (1957), however, did not find that it constantly lowered sputum viscosity in vivo.

Inhalations were given to 6 patients for 15 minutes three times daily. Oxygen flowing through a ' Riddocillin ' aerolyser nebulised the solution, and the resultant mist was inhaled through the mouth. The flow could be stopped during exhalation. A similar technique was used when giving inhalations of trypsin and deoxyribonuclease. In no case was sputum viscosity lowered ; in 2 patients it was increased ; in 4 it remained unaltered. No untoward effects were observed.

Trypsin

Lysis and thinning of viscid mucopurulent or purulent secretions by means of proteolytic enzymes seems a logical procedure, though trypsin is not in theory the ideal enzyme to use, because it is chiefly a fibrinolysin and most sputa do not contain a high proportion of fibrin. However, Limber et al. (1952), Unger and Unger (1953), and Habeeb et al. (1954), among others, have claimed that inhalations of crystalline trypsin can thin and loosen sticky tenacious sputum.

7 patients were given such inhalations for one period of about thirty minutes each day. The crystalline trypsin (' Tryptar ') was dissolved in Sörensen's phosphate buffer solution. On the first day 75,000 units of trypsin were administered, on the second day 100,000 units, and on the third and subsequent days 125,000 units.

In 2 patients sputum viscosity was lowered ; in 1 it was increased ; in 4 it remained unaltered.

Some degree of irritation by the vapour was observed in nearly all patients. The aerosol can irritate the eyes, and mild transient hoarseness after the treatment is common. 2 patients became wheezy and dyspnœic after each inhalation, and coughed vigorously for a time, but their total sputum volume for the day was not more than slightly increased. Farber et al. (1954) have also observed considerable irritative effects with inhaled trypsin, which in their opinion outweigh its possible advantages. It seems possible that trypsin given in this way acts mainly as a respiratory-tract irritant, and that its chief virtue (if it can be so called) is that it thereby stimulates coughing.

Deoxyribonuclease

Theoretically this should be a more satisfactory proteolytic enzyme to use in patients with viscid sputa, for it acts on deoxyribonucleoprotein (D.N.P.), the component which chiefly accounts for the viscosity of purulent sputum (Armstrong and White 1950). Deoxyribonuclease is, however, less likely to be of use to patients with mucoid sputa, in which D.N.P. is not present to the same extent.

Armstrong and White (1950) found that deoxyribonuclease reduced the viscosity of purulent sputum in vitro, and thought that some clinical benefit was apparent in a few patients to whom this enzyme was administered in aerosol form. Farber et al. (1954) also noted some apparent decrease in sputum viscidity after deoxyribonuclease, but did not find the clinical benefit very impressive.

3 of our patients received twice-daily inhalations of deoxyribonuclease, which was made up in a solution, at pH 7·0, containing magnesium chloride, an obligatory activator, and peptone, which stabilises enzyme activity. The solution must be used at once, as its activity declines

rapidly at room temperature. 1 patient used on each occasion a solution containing 1·25 mg. of deoxyribonuclease, but the other 2 received only half this amount (0·625 mg. in each inhalation).

In no case was any significant change in sputum viscosity observed.

The 2 patients who received the smaller dosage experienced no untoward effects. The patient who had the larger dosage complained of some dyspnœa and burning in the chest after the inhalations. Two weeks after the treatment was completed he died in coma, and necropsy revealed multiple cerebral abscesses. From these abscesses, and from the widespread bronchiectatic abscesses in his lungs, the same organism, *Escherichia coli*, was obtained. It seemed not unlikely that the proteolytic activity of deoxyribonuclease played some part in facilitating the passage of organisms from the bronchi into the blood-stream, and we therefore did not feel justified in giving deoxyribonuclease to any more patients. Farber et al. (1954) also noted frequent side-effects, including hæmoptysis, after administration of deoxyribonuclease, but they were using larger doses. We agree with them in considering that this enzyme is not without danger, especially to patients with heavily infected and damaged lungs. On the other hand, its advantages seem to be doubtful.

Comparison of Expectorants

In comparing the various expectorants used, one with the other, no constant effect could be observed. In 4 patients, sputum viscosity remained almost constant, both in the control period and throughout the trials (fig. 1). In 3 patients the viscosity during therapy was consistently *higher* than it had been in the control period (fig. 2). In 1 patient all forms of treatment lowered the viscosity (fig. 3). In 1 patient the results were variable (fig. 4).

Sputum Volume

Although the object of this trial was primarily to observe changes in sputum viscosity, sputum volume was also measured, and it is of interest to note that the daily sputum output of every patient remained remarkably constant throughout the whole period of observation. This is of some value in confirming that the viscosity figures have not been influenced by variations in the patients' clinical condition, and it also supports the conclusion of Alstead (1939) that expectorants given intermittently do not significantly influence sputum output.

Discussion

The results of this trial lend no support to the belief that currently available expectorants, when administered in the usual intermittent manner, effectively lower sputum viscosity. Several workers have convincingly demonstrated such a decrease in vitro. This does not necessarily conflict with our findings, for in-vitro measurements are made when the drug is actually in contact with the sputum, whereas we were measuring the overall effect of intermittent therapy. Presumably, therefore, the effects of expectorants on viscosity are very transitory. Theoretically it might be possible to lower sputum viscosity effectively by giving continuous treatment, but this would only be practicable with such apparently benign substances as hot and cold steam. The traditional steam-tent can at least do no harm, whereas continuous mist. expect. would soon prove nauseating, and continuous enzyme inhalation might be positively dangerous.

It is of course possible—though it seems improbable—that the therapeutic effect of expectorants is wholly unrelated to sputum viscosity. This is a speculative matter with which we are not here concerned. Nevertheless, it is odd that medicaments whose therapeutic value is supported by so little objective evidence continue to be so popular with both doctors and patients. It seems unlikely that suggestion can entirely account for their remedial effect, though undoubtedly this is a potent factor. Most of our patients, all of whom were aware of the purpose of the trial, said at the end of it that they had noticed no particular benefit from any of the drugs.

Summary

Various expectorants were administered in the usual intermittent way to patients, and the viscosity of their daily output of sputum was measured.

No evidence was found that such drugs given in this way effectively lower sputum viscosity.

We are indebted to Monsanto Chemicals Ltd. for supplies of 'Triton W.R.1339,' to Armour Laboratories for aerosol 'Tryptar,' and to Dr. W. M. Fee, of Benger Laboratories Ltd., for the deoxyribonuclease. Our thanks are due to Mr. E. M. Seller, A.I.M.L.T., for technical assistance. The expenses of this trial were defrayed by a grant from the Wrexham, Powys and Mawddach Hospitals Management Committee.

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OXYTOCIC AND ANTIDIURETIC ACTIVITY IN BLOOD FROM THE CONSCIOUS SUBJECT

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In a previous investigation (Bisset et al. 1956) extracts of blood obtained from the internal jugular veins of patients under anæsthesia were assayed for oxytocic and antidiuretic activity. It was not known to what extent the levels of activity detected were influenced by the effects of anæsthetic drugs on the neurohypophysis. It has now been possible to obtain blood for assay from different parts of the cardiovascular system in the conscious subject. Dr. Sheila Sherlock and Dr. A. Dawson, of the Postgraduate Medical School of London, at Hammersmith Hospital, have provided us with samples of blood collected during cardiac catheterisation from unanæsthetised patients. All of the six cases which were available were under investigation for hepatic cirrhosis or infective hepatitis. Although the series is small the results provide a pointer to future work.

Methods

Collection of Blood Samples

One patient (case 1 in the accompanying table) was given an injection of pethidine before cardiac catheterisation; none of the others received premedication. Samples were withdrawn either by cardiac catheter from the internal jugular vein and bulb, the superior vena cava and the right atrium or by puncture of the median cubital vein and the femoral artery.

Blood from the internal jugular vein or the superior vena cava will be designated "central," and from the remaining sites, "peripheral." From each patient a sample of "central" blood was obtained, followed within 2 or 3 minutes by a sample of "peripheral" blood. To a 5 ml. sample of the "peripheral" blood oxytocin ('Pitocin,' Parke Davis & Co.) 100 mU, or vasopressin ('Pitressin,' Parke, Davis & Co.) 10 mU was added to serve as a control for the recovery of activity in

ENDOGENOUS OXYTOCIC AND ANTIDIURETIC ACTIVITY IN CENTRAL AND PERIPHERAL BLOOD FROM CONSCIOUS PATIENTS AND RECOVERY OF ADDED HORMONE

Case	Sex	Age (yr.)	Condition	Endogenous activity in the blood						Recovery of added hormone
				Central			Peripheral			
				Source	O	A	Source	O	A	
1	F	56	Cirrhosis	I.J.V.	1·2	<0·003	F.A.	0·2(0·6)	<0·003	42%
2	M	45	Infective hepatitis	I.J.B.	0·3	<0·007	M.C.V.	0·1(0·3)	<0·008	78%
3	M	56	Cirrhosis (?amyloidosis)	I.J.B.	0·0(0·6)	<0·003	R.A.	0·0(0·2)	<0·004	N.E.
4	M	40	Cirrhosis with ascites	I.J.B.	0·1	0·023	M.C.V.	<0·3	<0·013	43%
5	F	52	Cirrhosis	S.V.C.	<0·4	<0·014	M.C.V.	<0·5	<0·015	44%
6	F	45	Cirrhosis with ankle œdema	I.J.V.	0·6(1·1)	0·019	M.C.V.	0·4(1·4)	<0·003	83%
		Mean			<0·4	<0·012		<0·3	<0·008	58%

O = oxytocic activity in terms of oxytocin (mU per ml.).
A = antidiuretic activity in terms of vasopressin (mU per ml.).
I.J.V., I.J.B. = internal jugular vein or bulb.
M.C.V. = median cubital vein.
S.V.C. = superior vena cava.
F.A. = femoral artery.
R.A. = right atrium.
N.E. = not estimated.

the extracts. The blood was collected in siliconed glass syringes (Bisset and Lee 1956) containing a trace of heparin 5000 U per ml. and delivered at once into nine volumes of acid alcohol in a polythene beaker.

Preparation of Extracts

The samples of blood in acid alcohol were taken for extraction from Hammersmith Hospital to Charing Cross Hospital Medical School. This involved a delay of about an hour in centrifuging the samples to remove the precipitated plasma proteins. Extracts were prepared from the supernatants by an improved method (Bisset and Lee 1957).

Assay of Extracts

In the previous investigation pituitary (posterior lobe) extract ('Pituitrin,' Parke Davis & Co.) was used as the standard for both oxytocic and antidiuretic assays. It has since been shown by Ginsberg (1956) that pituitrin, which is assayed for oxytocic activity only, has a relatively low and variable antidiuretic potency when given by intravenous injection in rats. It was therefore decided in the present investigation to use separate principles for assays, i.e., oxytocin (pitocin) for oxytocic, and vasopressin (pitressin) for antidiuretic, activity.

In a preliminary experiment it was found that pitocin and pituitrin did not differ by more than 10% in their oxytocic activity on the isolated uterus of the rat. In the case of oxytocic assays, therefore, comparisons of the results obtained with these two different standards is valid.

The methods of assay were the same as those used previously (Bisset et al. 1956).

Results

The results of assays of endogenous oxytocic and antidiuretic activity in "central" and "peripheral" blood, and the recoveries of exogenous activity, are shown in the table. The mean recovery of exogenous oxytocin (cases 1, 4, 5, and 6) or vasopressin (case 2) extracted from "peripheral" blood was 58%. Concentrations of endogenous activity are expressed in terms of oxytocin and vasopressin and have not been corrected for loss of activity on extraction.

In most cases oxytocic activity amounted to less than 1·0 mU per ml. To assay such small amounts is difficult. If, for example, 20·0 ml. blood containing 1·0 mU per ml. of oxytocic activity are concentrated to 3·0 ml. of extract, and half is used for the antidiuretic assay, there remains for the oxytocic assay only 1·5 ml. of an extract containing less than 7·0 mU per ml. Of this 1·5 ml., 0·5 ml. is required for treatment with sodium thioglycollate in order to detect any non-specific activity due to substances other than oxytocin. Unless the test preparation is particularly sensitive, it may be possible to state only the upper limit of activity, and this is indicated in the table by the symbol <. In those cases in which activity was not abolished by sodium thioglycollate the non-specific activity has been deducted from the total activity, and the latter is shown in parentheses.

The mean concentrations of oxytocic activity were <0·4 mU per ml. in "central," and <0·3 mU per ml. in "peripheral" blood. The corresponding values for antidiuretic activity were <0·012 and <0·008 mU per ml. In all cases except case 3 oxytocic activity was detected in both "central" and "peripheral" blood. Antidiuretic activity was detected in two cases, nos. 4 and 6, but in "central" blood only; the activity was abolished by sodium thioglycollate.

Discussion

It is assumed that in man the internal jugular veins provide the main drainage of the brain and pituitary gland. In the general circulation the neurohypophysial secretions are diluted and rapidly destroyed. If, therefore, the oxytocic and antidiuretic activity in blood extracts is due to the hormones of the neurohypophysis, the concentration should be higher in "central" than in "peripheral" blood.

In most of the present observations activity was either undetectable or present in too low a concentration to permit a valid comparison between "central" and "peripheral" blood. In case 1 however, in which the oxytocic activity in blood from the internal jugular vein exceeded 1·0 mU per ml. and could be assayed with some degree of accuracy, the concentration in blood obtained practically simultaneously from the femoral artery was only 0·2 mU per ml. It should be noted that this was the case in which the patient was given an injection of pethidine, a drug which is known to stimulate the neurohypophysis. In a parallel experiment which was carried out on an anæsthetised patient it was found that the concentration of oxytocic activity in blood from the internal jugular vein was 1·3 mU per ml. compared with 0·2 mU per ml. in blood obtained from the median cubital vein.

Antidiuretic activity was detected in only two cases (4 and 6): it was present in "central" blood only. In case 6 the ratio of the potency of "central" to that of "peripheral" blood was at least six, and was similar to the ratio observed in the case of oxytocic activity in case 1 and in the anæsthetised patient. These results, which provide evidence for the neurohypophyseal origin of the

activity in blood extracts, may be compared with those obtained in the rat by Ginsberg and Heller (1953). In this species the external jugular vein constitutes the main venous drainage of the pituitary gland. In conscious animals, antidiuretic activity was not detected in blood from the external jugular vein (<0·1 mU vasopressin per ml). In animals in which the neurohypophysis was stimulated by ether anæsthesia and by the withdrawal of successive samples of blood, activity was detected, and the concentration was found to be from 4 to 8 times greater than in blood from the carotid artery.

In the previous investigation (Bisset et al. 1956) blood was obtained from the internal jugular veins of patients under anæsthesia. The mean concentration of oxytocic activity was 1·2 mU per ml. (S.E. ±0·26). The value of <0·4 mU per ml. obtained in the present series of conscious subjects is significantly lower ($P<·05$), despite the fact that the recovery of activity in control experiments was greater (58% compared with 38%). These results confirm the view that the high levels of oxytocic activity previously reported may have been due to stimulation of the neurohypophysis by anæsthetic drugs.

It is interesting to note that in the two cases (4 and 6) in which antidiuretic activity was detected, either œdema or ascites was present. Whether or not the raised concentration of antidiuretic activity in "central" blood is causally related to the water retention is uncertain. The fact that activity was absent from "peripheral" blood suggests an increased secretion, rather than a decreased inactivation, of the hormone. This problem will be the subject of a further investigation.

It may be noted also that the high levels of antidiuretic activity in cases 4 and 6 were associated with low levels of oxytocic activity in the same samples of blood, whereas in case 1 the converse is true. These differences would suggest the possibility that vasopressin and oxytocin may be released independently from the neurohypophysis.

Summary

(1) Oxytocic and antidiuretic activity has been assayed in extracts of blood obtained from conscious subjects during cardiac catheterisation.

(2) The mean concentration of activity in "central" blood from the internal jugular vein or bulb, or the superior vena cava, was <0·4 mU per ml. oxytocin, and <0·012 mU. per ml. vasopressin. The corresponding figures for "peripheral" blood from the right atrium, the median cubital vein, or the femoral artery were <0·3 mU. per ml. oxytocin and <0·008 mU per ml. vasopressin.

(3) In cases in which a high concentration of oxytocic or antidiuretic activity was detected in "central" blood, activity in "peripheral" blood was either undetectable or present in very low concentration. This provides evidence in favour of the view that the activity detected in blood extracts is of neurohypophyseal origin.

(4) The mean concentration of oxytocic activity in "central" blood was significantly lower than that previously reported for patients under anæsthesia, suggesting that anæsthetic drugs may cause the release of oxytocin from the neurohypophysis.

(5) A dissociation between oxytocic and antidiuretic activities in the same samples of blood suggests the possibility that oxytocin and vasopressin may be released independently from the neurohypophysis.

We should like to express our gratitude to Dr. Sheila Sherlock and Dr. A. Dawson for their kindness in providing us with blood samples from their patients.

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THE EFFECT OF *d*-TUBOCURARINE CHLORIDE ON THE BLOOD-PRESSURE OF ANÆSTHETISED PATIENTS

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THE blood-pressure may fall after the intravenous injection of *d*-tubocurarine chloride in man (Albertson et al. 1956, Cullen 1943, Comroe and Dripps 1947, Doughty and Wylie 1951, Grob et al. 1947, Gray and Halton 1946, Harroun et al. 1947, Prime and Gray 1952, Whitacre and Fisher 1945). The fall occurs infrequently and is small, except when *d*-tubocurarine is used with deep anæsthesia (Whitacre and Fisher 1945, Comroe and Dripps 1947), with fluorinated hydrocarbons (Bryce-Smith and O'Brien 1956, Johnstone 1956), or in "sensitive" patients (Foldes 1957).

In my experience, however, the blood-pressure often falls after the use of *d*-tubocurarine in anæsthetised patients and the fall is sometimes large. I describe here an investigation undertaken to find out if such falls are due to *d*-tubocurarine and to assess their degree and incidence.

Method

After premedication with 'Omnopon' and scopolamine or with morphine and atropine anæsthesia was induced with 250–750 mg. of thiopentone sodium according to the age, weight, and clinical response of the patient, and continued with nitrous oxide (75%) and oxygen (25%) or with light cyclopropane and oxygen. Suxamethonium chloride was used when intubation was necessary and to provide relaxation pending the administration of *d*-tubocurarine (hereafter called curare). Respiration was controlled when inadequate.

Curare was given intravenously to 122 fit adult patients undergoing surgical operations (partial gastrectomy 29, cholecystectomy 12, herniorrhaphy 52, other abdominal operations 14, orthopædic operations 15).

The doses were chosen as being representative of those in common use. The number of patients receiving each dose is shown in the accompanying table.

The blood-pressure was measured in the arm, by the auscultatory method, at minute intervals. Curare

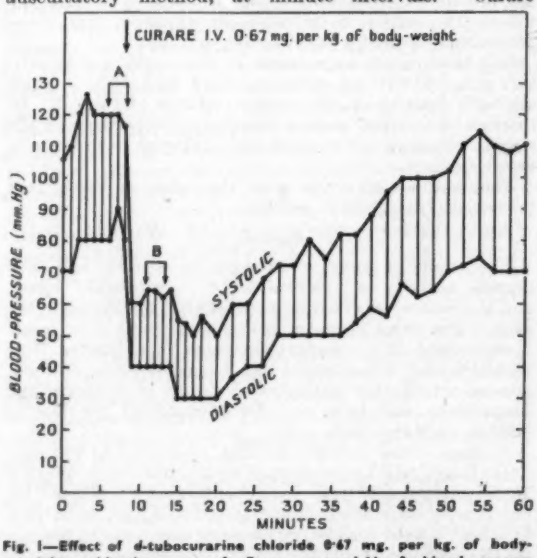

Fig. 1—Effect of *d*-tubocurarine chloride 0·67 mg. per kg. of body-weight on blood-pressure of a fit woman aged 44: A, blood-pressure before curare taken as mean of three values; B, blood-pressure after curare taken as mean of three values.

DOSES OF *d*-TUBOCURARINE CHLORIDE AND BLOOD-PRESSURE CHANGES IN 122 FIT PATIENTS

Dose (mg.)	15	20	25	30	35	40
No. of patients	20	25	20	27	21	9
Change in systolic blood-pressure (mm. Hg):						
Mean	−5	−11	−19	−22	−28	−37
Range	From +14 to −24	From +8 to −46	From +8 to −42	From +4 to −60	From +11 to −53	From −8 to −67

was given when the systolic pressure had been steady for five minutes. The change in pressure was taken as the difference between the mean of the three observations immediately before injection (fig. 1A) and the mean of those at the third, fourth, and fifth minutes after injection (fig. 1B).

The age, sex, weight, and type of operation were recorded for each patient.

Results

The blood-pressure fell after the injection of curare in 105 (86%) of the 122 fit patients, was unchanged in 3, and rose in the remaining 14.

The systolic pressure was within normal limits in all the patients before curare was given. After injection it fell to below 80 mm. Hg in 22% of the patients, to below 70 mm. Hg in 10%, and to below 60 mm. Hg in 3%.

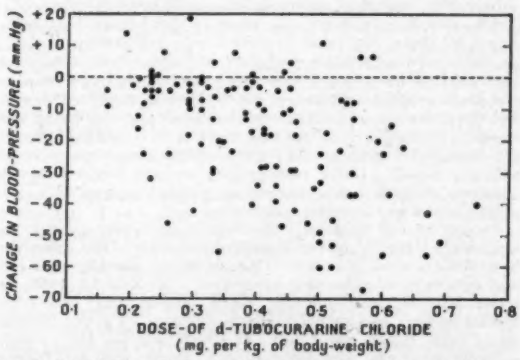

Fig. 2—Relationship between dose of d-tubocurarine chloride and change in systolic blood-pressure in 116 fit patients.

The fall in pressure began within one or two minutes of injection and reached a maximum within two to five minutes. Recovery was rapid if the fall was small, but prolonged if it was large (fig. 1).

The mean fall in pressure increased with the dose (see table), although individual response was variable (fig. 2). The change was not significant in the 15 mg. group, but it was when the dose was 20 mg. ($t = 2{\cdot}05$, $0{\cdot}05 > p > 0{\cdot}02$) or larger.

There was a direct relationship between the dose of curare, within the limits of 0·1–0·75 mg. per kg. of body-weight, and the amount of fall in systolic pressure (correlation coefficient $r = 0{\cdot}52$, $p < 0{\cdot}001$, fig. 2). The results for 6 patients have been omitted here because their weights were not recorded.

The proportion of large falls (arbitrarily defined as 30 mm. Hg or more) was greater with doses of 0·4–0·75 mg. per kg. of body-weight (24 of 58 patients) than with those of 0·1–0·39 mg. per kg. of body-weight (8 of 58 patients). The difference was significant ($\chi^2 = 13{\cdot}0$, $p < 0{\cdot}001$).

The diastolic pressures fell in much the same way. The results have not been tabulated because they were incomplete.

In the 14 ill patients the fall in pressure was larger: 15 mg. (0·2–0·33 mg. per kg. of body-weight) produced a mean fall in systolic pressure of 31 mm. Hg; the range of effect was +13 to −73 mm. Hg; and the fall was greater than 30 mm. Hg on eight occasions.

In the 20 patients who were given suxamethonium 50 mg. the mean change in pressure was +0·6 mm. Hg, and the range +19 to −20 mm. Hg. This change was not significant.

Discussion

It may be argued that the observed falls in blood-pressure could have been due to controlled respiration or to other factors—e.g., surgical manipulation—rather than to the curare. The first possibility is unlikely because no significant fall followed control of respiration in patients paralysed with suxamethonium and the pressure after curare returned to its previous level while the respiration was still being controlled. Other factors are also unlikely to be responsible because the fall always appeared within one or two minutes of the injection.

In spite of the correlation between the dose of curare and the amount of fall in blood-pressure a feature of the results was the wide variation in response from patient to patient. A detailed analysis of the data suggested that, although the patients' age, the site of operation, and whether or not suxamethonium was given before the curare might have influenced the response, these factors were not enough to explain the wide range of individual susceptibility.

This investigation gives no information about the mechanism by which curare produces hypotension. Pharmacological evidence suggests that the most likely causes are histamine release (Alam et al. 1939, Brown 1947, Comroe and Dripps 1946, Grob et al. 1947, Landmesser 1947, Mongar and Whelan 1953, Sniper 1952) and autonomic ganglion block (Everett 1948, Guyton and Reeder 1950, Luco and Altamirano 1943, Luco and Mesa 1941, Mautner and Luisada 1941).

Summary

Blood-pressure changes following the intravenous injection of *d*-tubocurarine chloride 0·1–0·75 mg. per kg. of body-weight were studied in 122 fit patients and in 14 ill ones.

The pressure fell in 117 of these, the fall being relatively greater in the ill patients.

Dose and blood-pressure fall were significantly correlated, but there was considerable variation between individual responses to the same dose.

Reasons are given why the fall is due to a specific effect of the curare.

I wish to thank Dr. H. J. V. Morton for helpful advice and criticism.

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HÆMOGLOBINURIA AND ACUTE HÆMOLYTIC ANÆMIA ASSOCIATED WITH PRIMARY ATYPICAL PNEUMONIA

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ACUTE hæmolytic anæmia complicating primary atypical pneumonia, and usually associated with high-titre cold agglutinins, is comparatively uncommon. However, of recent years there has been an increasing number of reports of this complication.

Antopol et al. (1939) reported 2 patients with acute hæmolytic anæmia associated with cold auto-agglutinins: one patient had pneumococcal lobar pneumonia; and both had received sulphonamide therapy.

Dameshek (1943) described 2 patients with acute hæmolytic anæmia associated with atypical (virus) pneumonia. Potent cold agglutinins were present with maximal activity at 3°C, some activity at room-temperature, and little or no activity at 37°C. The patients were treated with sulphonamides, which were considered to be responsible jointly with the cold agglutinins for the hæmolysis.

Similar cases were described by Horstmann and Tatlock (1943) and Peterson et al. (1943), who established the presence of cold agglutinins, usually in high titres, in most cases of atypical (virus) pneumonia.

Ginsberg (1946) described the first case of acute hæmolytic anæmia developing during the course of severe primary atypical pneumonia with a high titre of cold agglutinins in a patient who had not been treated with sulphonamides.

Besterman and Brigden (1949) reported the first such patient in this country and collected 25 other published cases.

Since then there have been further reports of similar cases, and Dacie (1955) has investigated the sera of 8 such patients.

From these reports it appears that hæmolysis associated with atypical pneumonia usually develops at the end of the second, or in the third, week of the illness. The onset is usually sudden, and the patient, who has almost recovered from his respiratory infection, becomes very ill again, with increasing pallor, jaundice, and often pyrexia. The liver may be palpable, but the spleen is less often felt; anæmia is usually severe, and leucocytosis, with some primitive cells in the peripheral blood, is nearly always present. The serum-bilirubin level is raised, and the plasma-hæmoglobin level also is usually above normal. Urobilinogen is present in excess in the urine, and there is sometimes frank hæmoglobinuria. Auto-hæmagglutination at room-temperature is striking and invariable. The auto-agglutinins are always of the cold variety, with titres that may rise to 1 : 32,000.

We report here a further case partly because of the striking mode of presentation (hæmoglobinuria) and partly because the Donath-Landsteiner reaction was positive, which is unusual.

Case-report

A man, aged 52, felt unwell on April 12, 1955, and next day had a severe cough, with general malaise and night sweats. After three days in bed he felt sufficiently well to move house. On April 27, 1955, he consulted his doctor, complaining of shortness of breath, a cough with sputum, and weakness. He was apyrexial, and presented no abnormal physical signs. His sputum was mucopurulent and slightly bloodstained, and *Streptococcus viridans* was cultured from it, together with scanty growths of monilia and *Neisseria catarrhalis*. On April 29, 1955, his temperature rose to 101·2°F, and treatment with 'Estopen' 500,000 units daily was started; no sulphonamides were given. After three days he became apyrexial and the infection of his respiratory tract was improving. On the night of May 3, 1955, his urine, which had previously been normal in colour, was deep red. Next morning he was jaundiced, but in the evening his urine was paler. On the morning of May 5, 1955, his skin and conjunctivæ were pale light yellow, his tongue was furred and there were basal râles in his chest, with some scattered bronchospasm. His blood-pressure was 120/80 mm. Hg; his liver and spleen were impalpable, and his urine had the colour of dark mahogany. He had had no serious illness in the past. He was admitted to hospital on the evening of May 5, 1955, because his general practitioner had reported that his condition had deteriorated since the morning.

On examination the patient was apyrexial but obviously very anæmic. A sample of urine obtained soon after admission was dark red, sp. gr. 1·020, and contained albumin and blood (chemical test). Subsequent analysis of this urine showed an excess of urobilinogen together with methæmoglobin; there was no bilirubin. A specimen of blood taken on admission by the usual technique was grossly hæmolysed. Another specimen was then taken into a syringe warmed to 37°C and did not appear hæmolysed to the naked eye. The plasma was icteric and slightly brown; this was shown to be due to methæmalbumin. The hæmoglobin was 4·8 g. per 100 ml., red blood-cells 1,400,000 per c.mm., packed-cell volume 15%, mean corpuscular volume 107 c.μ., mean corpuscular hæmoglobin concentration 32%, and reticulocytes 7%. A blood film showed normochromia and anisocytosis; there were 37,800 white blood-cells per c.mm. (neutrophils 79%, lymphocytes 17%, monocytes 4%). The blood-group was A, rhesus-positive, the erythrocyte-sedimentation rate (E.S.R.) 156 mm. in 1 hour (Westergren), blood Wassermann reaction negative, and cold agglutinin titre 1 : 1024. The Donath-Landsteiner reaction was positive and Coombs test positive (cells separated and washed at 37°C). Microscopy of the urinary deposit revealed a moderate number of red blood-cells, many leucocytes, and granular casts; culture of the urine and the blood was sterile. Culture of the sputum gave a very scanty growth of β-hæmolytic streptococci; three cultures were negative for tubercle bacilli. Chest radiography showed small irregular opacities at both bases, suggesting patchy pneumonitis, and some fibrosis in the right upper zone.

Treatment and Progress.—On May 7, 1955, the patient was transfused with $3^1/_2$ pints of packed red cells. His urine was now quite normal in colour. He improved steadily after this and two days later became apyrexial. On May 12, 1955, his chest still showed bilateral basal crepitations and some bronchospasm, but his hæmoglobin was now 7·5 g. per 100 ml., white cells 11,500 per c.mm., and reticulocytes 10%. Subsequent progress was uneventful: there was no further hæmoglobinuria, and the blood-count gradually returned to normal. He was treated with cyanocobalamin 1000 μg. twice weekly and ferrous sulphate gr. 6 t.i.d. and was discharged symptom-free on June 10, 1955, when radiography showed that the left base was now clear and the right base almost clear, his hæmoglobin was 11·5 g. per 100 ml., and the Donath-Landsteiner reaction was still positive.

Follow-up.—On July 12, 1955, he was symptom-free and presented no abnormal physical signs; his urine was clear yellow and contained no albumin. Radiography showed that his lung fields were clear except for the fibrosis at the right apex. His hæmoglobin was 13·8 g. per 100 ml., white cells 7100 per c.mm., E.S.R. 33 mm. in 1 hour (Westergren); the Donath-Landsteiner reaction and Coombs test were still positive.

Donath-Landsteiner Test

The Donath-Landsteiner cold antibody is unique in its mode of action. Thus, though it is a true cold antibody in that it only attaches itself to the red cells at temperatures well below 37°C, the hæmolysis due to the antibody only takes place when the blood is rewarmed to 37°C in the presence of complement. All other types of cold hæmolytic antibodies cause hæmolysis when the blood is cooled.

In our patient the degree of cooling required to render the Donath-Landsteiner reaction positive altered with time. Thus, on admission, cooling of the blood to room-temperature (21°C) was sufficient because the blood was grossly hæmolysed on being rewarmed. Later, it was necessary to cool the blood to 17°C before hæmolysis occurred on rewarming. On July 12, 1955, to elicit a positive Donath-Landsteiner reaction it was necessary to

cool the blood to 7°C for hæmolysis to take place on rewarming. A year after the patient had been discharged from hospital, both the Donath-Landsteiner reaction and the Coombs test were negative.

Discussion

Hæmoglobinuria is an uncommon development in the hæmolytic anæmia associated with atypical (virus) pneumonia. Probably the speed and severity of the hæmolytic process are the determining factors: the more rapid the process the more likely it is that the renal threshold for hæmoglobin is exceeded and hæmoglobinuria results.

Various suggestions about the mechanism of this hæmolytic process have been made.

(1) Stats (1945) showed that, in the presence of cold agglutinins, the red cells have an increased mechanical fragility. He suggested that hæmolysis might be due to trauma in the circulation, but against this theory is the fact that many patients with high-titre cold agglutinins do not have hæmolytic anæmia. However, the harmful effect of chilling patients with high-titre cold agglutinins is well illustrated by the patient described by Colmers and Snavely (1947) in whom acute hæmolytic anæmia followed sponging with cold alcohol. These workers later demonstrated local hæmolysis in this patient when the arm was immersed in cold water.

(2) A second possibility is suggested by Dacie (1949, 1950, 1955), who showed that patients with high-titre cold agglutinins and hæmolytic anæmia also have a cold hæmolysin which is most active at a lower pH than that normally found in the plasma; hæmolysis could be demonstrated readily in such cases in vitro by acidifying the serum. Dacie also found that there was no good correlation between the height of the titre and the development of hæmolysis, but he has suggested that the highest temperature at which the cold hæmolysin is active is more important in determining hæmolysis than the titre in the cold.

(3) A third mechanism of hæmolysis is due to the absorption or fixation of the virus on to the patient's red cells, which are then destroyed together with the virus by the patient's antibodies, as suggested by Moolten et al. (1953) in the case of the virus of Newcastle disease.

(4) Our patient represents a fourth possible mechanism, because hæmolysis followed rewarming of the blood after chilling, the Donath-Landsteiner reaction being positive. It seems likely that the patient was chilled during the ambulance journey to hospital, and that hæmolysis took place when the cooled peripheral blood entered the circulation again. The only other reported case with a positive Donath-Landsteiner reaction is the patient described by Neely et al. (1951), in whom it was "slightly positive": agglutination and some hæmolysis took place when the blood was chilled, hæmolysis being more severe on warming. Hæmolysis, however, was by no means complete.

Dacie's suggestion that the thermal amplitude of the activity of the hæmolysin is more important than the height of the titre of the cold agglutinin is confirmed by the present case. Thus, at first, cooling the patient's blood to a temperature of 21°C and rewarming caused hæmolysis in vitro; at this stage the patient had hæmolytic anæmia with hæmoglobinuria. When, some weeks later, it was necessary to cool the blood to 7°C before hæmolysis took place in vitro on rewarming, the patient presented no clinical evidence of hæmolysis.

The present case and that of Colmers and Snavely (1947) illustrate the advisability of avoiding chilling in the management of atypical (virus) pneumonia, particularly if there is a high titre of cold agglutinins, because there is a definite risk of precipitating acute hæmolysis.

Summary

A patient with hæmolytic anæmia secondary to atypical virus pneumonia is described, in whom the presenting symptom was hæmoglobinuria. Cold agglutinins were present in a titre of 1 : 1024, and the Donath-Landsteiner reaction was positive. The thermal amplitude of the activity of the cold antibody in vitro correlated well with the development of hæmolysis in the patient.

The possible factors involved in the hæmolytic process are discussed, and it is suggested that chilling patients with a high titre of cold agglutinins is most undesirable because it may precipitate hæmolysis.

Our thanks are due to Dr. G. E. Beaumont for permission to publish details of his patient and for encouragement and advice.

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Preliminary Communications

RENAL CLEARANCE OF FREE AND CONJUGATED 17-HYDROXYCORTICOSTEROIDS IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

THE adrenal cortex is now thought to play a large part in maintaining arteriolar tonus, and total adrenalectomy has been shown to cause a dramatic remission of malignant hypertension.[1] But the relation between high blood-pressure and the secretion of adrenocortical hormones has not yet been elucidated.

Several workers [2] have studied the levels of corticoids in the plasma of hypertensive patients, and their urinary secretion; but no significant changes have been found. Analysis of the methods used in these investigations reveals that only the "free" fraction of corticoids was estimated in blood, whereas the "total" (free and conjugated) corticoids were measured in urine.

In the present work the free and the conjugated 17–hydroxycorticosteroids (17-OH-CS) in blood and urine were estimated separately, thus allowing the separate determination of the renal clearance of endogenous free and conjugated 17-OH-CS.

METHODS

The methods developed and used in this work are to be published in detail elsewhere.[3] They have been based on the Porter-Silber [4] colour reaction, and a butanol-chloroform mixture was used for extracting the conjugated 17-OH-CS. The reproducibility of the methods is best expressed by the coefficient of variation, which was 2·2% in the method for free 17-OH-CS, and 2·4% for urine and 5·0% for plasma in the method for conjugated 17-OH-CS.

One-hour renal clearance of 17-OH-CS was determined, free and conjugated steroids being estimated separately, in 12 normotensive people (most of them members of the staff) and in 11 patients with essential hypertension. To minimise possible differences due to diurnal variations, most of the tests were made between 9.30 A.M. and 10.30 A.M. (A preliminary investigation revealed that one-hour clearance gave the most reproducible results.) The tests were made on a slightly falling diuresis, the patients drinking 200 ml. of water fifteen minutes before

1. Arnott, W. M., Crooke, A. C., Donovan, H., Taylor, S. H. *Quart. J. Med.* 1957 (in the press).
2. Hetzel, B. S., Hine, D. C. *J. clin. Endocrin.* 1952, **12**, 296. Perera, G. A. *Bull. N.Y. Acad. Med.* 1950, **26**, 75. Genest, J. Symposium on Hypertension; London, 1954, p. 203.
3. Kornel, L. In the press.
4. Porter, C. C., Silber, R. H. *J. biol. Chem.* 1950, **185**, 201.

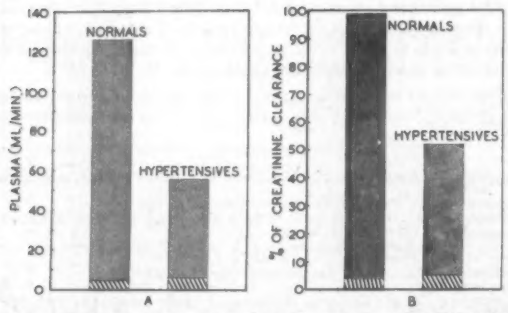

Fig. 1—Mean values of renal clearance of free and conjugated 17-OH-CS in normotensive and hypertensive subjects. A, absolute values. B, values related to creatinine clearance. Lower part of each histogram, free 17-OH-CS; upper part of each histogram, conjugated 17-OH-CS.

the first emptying of the bladder. Creatinine clearance was examined simultaneously, the method of Løken [5] being used for the estimation of creatinine in serum and urine.

RESULTS

No substantial difference was found between the renal clearances of the free 17-OH-CS in the two groups of people (normotensive and hypertensive). The clearance of the free 17-OH-CS in normotensives ranged between 2·7 and 9·2 ml. of plasma per minute (mean 4·6 ml.) and in hypertensives between 1·9 and 9·6 ml. (mean 5·7 ml.). Considerable differences, however, were detected in the renal clearance of the conjugated 17-OH-CS (see figure). In normotensives the conjugated 17-OH-CS were cleared at a rate of 90–189 ml. of plasma per minute (mean 126 ml.), in hypertensives at a rate of 31–90 ml. (mean 55 ml.). Thus the clearance of the conjugated 17-OH-CS was significantly lower in the hypertensives than in the normotensives. It was lower in those hypertensives whose renal function was normal as judged by other tests, including the creatinine-clearance test. In all the hypertensives with renal damage the decrease in the clearance of the conjugated 17-OH-CS exceeded the decrease in creatinine clearance. The decrease in clearance of the conjugated 17-OH-CS raised their level in the blood, altering the ratio of free to conjugated 17-OH-CS in the blood. The mean of this ratio was 1·0/1·1 in the normotensives and 1·0/2·2 in the hypertensives.

The renal clearance of 17-OH-CS glucuronides (using β-glucuronidase hydrolysis) was determined simultaneously with that of the total conjugated 17-OH-CS in a second series of normotensives and hypertensives. The 17-OH-CS glucuronides were cleared at similar rates in the two groups of people. Moreover, the levels of the total conjugated 17-OH-CS in the urines of the hypertensives were almost identical with the levels of the 17-OH-CS glucuronides in the same specimens.

DISCUSSION

Are the detected differences primary or secondary to the renal damage? It could be argued that, even in cases with normal creatinine clearance, there may be a selective impairment of the renal function as regards certain substances, including conjugated 17-OH-CS. On the other hand, though very little is known about the factors regulating the glomerular filtration and the tubular reabsorption or the excretion of corticoids, selective impairment seems unlikely.

The fact that the patients with essential hypertension seem to lack conjugated 17-OH-CS other than glucuronides in their urines supports the possibility that this is a primary change. These conjugated 17-OH-CS may be retained in the circulation because of the formation of a triple complex with another substance (more firmly bound with proteins or polypeptides) which is too big to be cleared by the kidney. An alternative possibility is that in patients with essential hypertension the other conjugates (presumably sulphates) are either not synthesised or synthesised at a much lower rate.

These questions are under investigation at present, as well as a possible change in the renal clearance of the endogenous 17-OH-CS when their levels are increased by stress or by corticotrophin. It is hoped that the solution of these problems will throw more light on the nature and the mechanism of the hypertensive diseases.

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5. Løken, F. *Scand. J. clin. Lab. Invest.* 1954, 6, 325.

New Inventions

MODIFICATION OF POLYETHYLENE CATHETER FOR INTRAVENOUS INFUSIONS

THE use of a polyethylene catheter has simplified the giving of continuous intravenous infusions to small infants, but there is a weakness in the methods of connecting the transfusion set to the catheter. The screw-down metal adapters which grip the polyethylene by compression of a rubber washer are heavy, drag on the catheter, and contain large dead spaces in which the red cells sediment, necessitating frequent adjustment of the drip regulator to maintain a constant drip-rate. Alternatively, a serum or hypodermic needle with the point cut off is pushed into the lumen of the polyethylene catheter as an adapter. The lumen of the adapter is then the narrowest point in the drip system and, if only a fine catheter can be introduced into the vein, this narrow lumen may not permit sufficiently rapid drip-rates.

To prevent the adapter needle from reducing the lumen of the catheter a 2-inch length of larger-size polyethylene

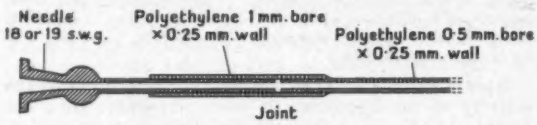

Fig. 1

tubing can be used as an outer sleeve, the adapter being inserted into one end and the catheter into the other (fig. 1). This does not create a watertight and airtight connection between the two pieces of polyethylene, and no satisfactory plastic cement for joining two pieces of polyethylene has yet been found; but this junction can be bonded by heat and the union made strong enough to withstand sterilisation by boiling.

Method of sealing

The two polyethylene tubes are united by melting the outer tube on to the inner after 2 inches of the outer tube has been pushed over the inner for about $^1/_8$–$^1/_4$ in. A

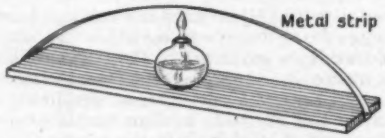

Fig. 2

thin wire is inserted for about 1 in. beyond the join to prevent the tubes from collapsing during sealing.

The joint can then be gently and repeatedly stroked with a heated strip of flat metal about 1/4 in. wide until the large tube melts to seal on to the smaller tube. This method is tedious, and it is better if the heated strip of metal is supported across the spirit-lamp flame, leaving both hands free to manipulate the polyethylene.

A strip of 22 S.W.G. brass 1/4 in. wide is bent to form a semicircle, and each end is screwed to the ends of a wooden base-board (fig. 2). A spirit-lamp stands on the base-board and warms the metal strip. The polyethylene tube can then be held in both hands while the joint is rotated against the warm metal at the point of optimal temperature.

Care and experience are required because the temperature at which the tube melts and bonds on to the smaller tube is easily exceeded. Close attention should be paid to the end of the large tube; if this is moulded down to a fine bevel, a leak-proof joint is more certain. If the tubing becomes too soft it should be kept revolving on the metal strip further away from the heat of the flame.

To test for leakage methylated spirit is squirted through the tube under pressure while the walls of the far end of the catheter are pinched together.

Injections into Catheter

A further difficulty in the use of a polyethylene catheter is that when anæsthetists wish to use the transfusion as a vehicle for administering drugs during operations on small infants, the injection of such drugs into the tubing close to the vein irritates the surgeon by disturbing the sterile coverings; the anæsthetist by the delay in the drug reaching the vein; and the pædiatrician by the frequent clotting and stoppage of the transfusion induced by the irritant injection.

This problem has been overcome by using a polyethylene catheter 3 ft. long and bringing the end of the catheter right up to the head of the table. A two-way adapter is introduced between the polyethylene and the drip tubing. The anæsthetist can then inject his drugs directly down the catheter and wash them into the vein with a small volume of either saline solution or blood before switching back to the normal transfusion. This technique has reduced significantly the number of occasions in which a transfusion has become blocked during operations on very small infants.

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Reviews of Books

Medical Treatment

KENNETH MACLEAN, M.D., F.R.C.P., assistant director, department of Medicine, Guy's Hospital, London. London: J. & A. Churchill. 1957. Pp. 696. 50s.

ADVANCES in therapeutics during the past twenty years have been so rapid and extensive that books dealing almost exclusively with medical treatment have firmly established themselves. New drugs are now introduced with such speed, and under so many bewildering names, that it is hard to preserve a reasoned judgment of their worth. Dr. MacLean is therefore to be congratulated on this eminently reliable account of modern treatment. The house-physician, his seniors on the hospital staff, and the general practitioner will particularly appreciate the precise instructions about how to give drugs and manage patients. And the medical student who consults Dr. MacLean's views as he reads up his clinical cases will be much the wiser; and he will also profit from the general sections on fluid and electrolyte disturbances, steroid drugs, and antibiotics.

In modern clinical practice many treatments still have no reliable scientific basis, and some of them had inevitably to be described in this book. Some account would be welcome of the principles and difficulties of assessing in man the value of many forms of treatment. A new edition of this valuable book will certainly be needed before long, and it might then be possible to add such a chapter.

A Synopsis of Otorhinolaryngology

JOHN F. SIMPSON, F.R.C.S., consultant surgeon, ear, nose and throat dept., St. Mary's Hospital, London, and Paddington General Hospital, IAN G. ROBIN, F.R.C.S., consultant surgeon, ear, nose, and throat dept., St. Mary's Hospital, London, and Royal Northern Hospital; J. CHALMERS BALLANTYNE, F.R.C.S., honorary first assistant, ear, nose, and throat dept., St. Mary's Hospital, London, consultant surgeon, ear, nose, and throat dept., Royal Northern Hospital, and assistant director, audiology unit, Royal National Throat, Nose, and Ear Hospital, London. Bristol: John Wright. 1957. Pp. 443. 42s.

IN its intention of providing quick reference, particularly for those studying for postgraduate examinations, this book is entirely successful, and the whole subject is surprisingly fully covered in under 450 pages.

The introductory chapters on anatomy and physiology are brief and clear, particularly underlining the details relevant to surgical technique and clinical understanding. Numerous line drawings emphasising the more important points are a valuable feature, and they are especially useful in the chapters on radiology, where students' difficulties are resolved by showing the principal views alongside the appropriate positions of the head.

A synoptic style often gives a uniform emphasis, making it hard to separate the common and important conditions from the less common, so that the book's practical value in clinical matters is limited. For instance, when dealing with acute otitis media, the fact that this is predominantly a disease of children and a common complication of measles is not at once apparent. In other sections various methods of treatment are listed rather impartially without necessarily giving the authors' views about their respective merits.

The preparation has clearly entailed much reference to modern literature, and future editions could usefully be enriched by the inclusion of a bibliography at the end of the chapters.

Dr. C. H. Edwards' useful concluding section on neurology of the ear, nose, and throat deals not only with intracranial complications in otorhinolaryngology but also with headache, facial pain, vertigo, and speech disorders.

Rheumatic Diseases, Rheumatism and Arthritis

HEINRICH G. BRUGSCH, M.D., assistant professor of medicine, School of Medicine, Tufts University. Philadelphia: J. B. Lippincott. London: Pitman Medical Publishing Co. 1957. Pp. 330. 80s.

TO write a short guide to the rheumatic diseases is a difficult task, and a really satisfactory book has yet to be written. Some conditions are still too poorly defined for crisp description and avoidance of controversy (Dr. Brugsch's section on fibrositis illustrates these difficulties).

Chapters about individual conditions, which are well described, are preceded by chapters on drug therapy, physical methods of treatment, and laboratory tests. Some of the material is redundant—thus, the techniques of massage are described in detail, but indications for their use are omitted. To get a clear picture of the practical management of rheumatoid arthritis (the basic régime of rest, splints, drugs, exercises, and reablement), the reader must consult several sections of the book. The radiographs are reproduced only just well enough to illustrate their points.

Some of the therapeutic advice is irrational: thus, in the management of gout, salicylic acid is recommended for periods of not more than one to two months, while for probenecid the modern view of continuous treatment with a uricosuric drug is accepted. In rheumatoid arthritis it is hard to see what value lies in splints which are "removed several times a day"; and many clinicians would question the use of corticotrophin or cortisone in relatively short courses.

There are some small but regrettable inaccuracies: for example, in dermatomyositis an increased secretion of creatine, not creatinine, is the important abnormality; and miner's elbow, tennis elbow, and olecranon bursitis are not synonymous.

Orthopædic Surgery in Infancy and Childhood

A. B. FERGUSON, JR., M.D., A. B. FERGUSON, SR., M.D., J. S. DONALDSON, M.D., W. F. DONALDSON, M.D., ROBERT KLEIN, M.D., F. H. STELLING, M.D. Baltimore: Williams & Wilkins. London: Baillière, Tindall, & Cox. 1957. Pp. 508. £6.

WHEN, in 1741, Nicolas André of Paris wrote his beautifully illustrated treatise, *Sur l'orthopédie*, the word he coined was synonymous with the study of deformities in children. The term now denotes much more, but, considering how many disorders of the locomotor system in adults have their origin in childhood, it seems strange that comparatively few works have since been written on purely pædiatric orthopædics.

This volume, by six leading American physicians and surgeons, will be received everywhere with much interest. In a comprehensive and detailed way it deals with its subject on a regional plan, with supplementary chapters on the generalised affections of bone and muscle, neoplasms, and diseases of the central nervous system. The section concerned with "the upper extremity" is particularly interesting for its descriptions of the congenital anomalies of the hand and of such conditions as "wringer arm," usually to be found only in specialised monographs.

Some important information, presumably made known too late for inclusion, is not mentioned. Thus, there is no account of anterolateral decompression in the section on tuberculous paraplegia, nor is the technique of the excision of damaged muscle described under Volkmann's contracture. Some British orthopædic surgeons will have their own views on various points: for instance, it is widely held, in this country, that transplantation of the tibial tubercle is not always a sufficient treatment for recurrent dislocation of the patella. But these are matters of opinion. On points of fact, it is a pity to find such a praiseworthy book blemished by the mis-spelling of the names of Pott and Denis Browne.

Here is a well-balanced, conservative, and authoritative guide to the recognition and management of all the common—and many of the rare—orthopædic disorders of children. Admirably produced and illustrated, it is likely to be widely read and acclaimed not only by orthopædic surgeons but also by pædiatricians.

Inhalation Analgesia in Childbirth

E. H. SEWARD, D.M., F.F.A.R.C.S., consultant anaesthetist, High Wycombe group of hospitals; R. BRYCE-SMITH, D.M., F.F.A.R.C.S., first assistant, Nuffield department of anaesthetics, University of Oxford. Oxford: Blackwell Scientific Publications. 1957. Pp. 58. 7*s*. 6*d*.

INHALATIONAL analgesia, an accepted part of midwifery practice in this country, has received a well-merited stimulus from the introduction of trichloroethylene to the ambit of the midwife. Even so, both trichloroethylene and the long-established nitrous oxide call for special apparatus, and some knowledge of basic principles on the part of the administrator, if the best results are to be achieved. Dr. Seward and Dr. Bryce-Smith describe these essential facts in a practical way, without undue detail and with emphasis on self-administered analgesia. The result is a valuable book which should be in every practising midwife's pocket, and which can give much guidance to doctors interested in these forms of analgesia.

The Treatment of Burns

CURTIS P. ARTZ, M.D., F.A.C.S., associate professor of surgery, University of Mississippi Medical Center; ERIC REISS, M.D., instructor in medicine, Washington University School of Medicine, St. Louis. Philadelphia and London: W. B. Saunders. 1957. Pp. 250. 52*s*. 6*d*.

CLEAR and concise presentation makes the most of wide clinical experience in this well-illustrated book full of practical information for surgeons treating burns. But the subject is so important and the book so readable that every medical student could study it with profit.

Since the authors at times express personal views, some differences of opinion are inevitable. The account of initial replacement therapy is generally well balanced, but there is little reference to the causes, diagnosis, and management of renal failure, with or without oliguria, and no mention of the value of red-cell-volume estimations after extensive deep burns. In the chapter on initial local care, some confusion seems to exist between the depth and intensity of burning. Greatly reduced pain-sensibility in the "pin-prick test" is surprisingly claimed to indicate full-thickness injury, and the red zone of stasis in the subcutaneous tissues, which is such a valuable guide to the depth of necrosis in early excisions, is not mentioned.

An excellent chapter on infection emphasises the frequency of fatal septicæmia. The problem of preventing cross-infection is not discussed, and its importance is perhaps overshadowed by too much emphasis on the normal bacteria in the skin appendages; many surgeons will feel more strongly about the duty of preventing added infection by pathogens not normally present in the skin.

One other feature deserves special mention—a brief but clear description of the emotional disturbances of the badly burned patient, and the part which the doctor and nurse should play in helping him to face his anxieties, his helplessness, and the physical ordeal. "The entire program of emotional rehabilitation is the direct responsibility of the attending physician." The awareness of this is as refreshing as it is rare in the vast literature on burns.

Animals Parasitic in Man

GEOFFREY LAPAGE, M.D. Harmondsworth: Penguin Books. 1957. Pp. 320. 5*s*.

THIS Pelican has three aims: to give a popular story of the more important animals which are parasitic in man; to set out the essential facts for medical students and the like; and to explain the general principles of parasitology.

The many excellent diagrams give lay readers a clear understanding of the complicated life-cycles of the parasites, and stimulate curiosity to read the text. Parasitology has a morbid fascination for the layman, and all the grim details are here for him to enjoy. He is led very cleverly on from the lone hands to those wonderfully differentiated creatures which need multiple hosts for their survival.

For examination purposes medical students must bring themselves to believe almost every word of the seemingly incredible life-cycles of our parasites, and this book can very well help them to do so. The diagrams make revision simple for those who depend on their visual memories.

The general principles of parasitology run as a theme throughout the book, but the later chapters collect and rearrange the basic factors, to lift the subject out of a fascinating little corner of zoology or pathology, and set it against the similar problems of the wider world—the struggles for food and existence, the interplay of hosts and parasites. However sterile may be our moon and other satellites, this planet remains a crawling mass of living creatures so strangely intolerant of symbiosis.

Occupational Diseases of the Skin (3rd ed. London: Henry Kempton. 1957. Pp. 981. £6 10*s*.).—Dermatologists and physicians of industrial medicine will welcome this new edition, after an interval of ten years, of what has become the standard reference book on occupational diseases of the skin. It is the work of three authors—Dr. Louis Schwartz, Prof. Louis Tulipan, and Prof. Donald J. Birmingham. The layout remains basically unchanged but the number of pages has been increased by 17. A vast array of new chemicals and new methods of manufacture have emerged since the last edition, and with them have come fresh skin hazards, both to the workers using them and to the general public who come in contact with products containing these chemicals. To meet these developments the authors have almost completely replaced the bibliography of the previous edition, and most of the present references date from 1943. An important addition is a chapter by W. D. Norwood on skin hazards from radiation in atomic industry, medicine, and warfare; and a chapter by Francesco Ronchese on occupational marks is also included.

World Medical Periodicals (New York: World Medical Association. 1957. Pp. 340. 30*s*. Obtainable in this country from the British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.).—Mr. L. T. Morton has again listed the world's journals concerned with medicine and allied sciences which are now appearing, as well as the important ones which have ceased publication since 1900. Many of the first edition's omissions have been repaired. Each entry gives a reference number, the title, the address of publication, and the title abbreviated according to a modification of the system used in the *World List of Scientific Periodicals*. There are indices of periodicals by country and by subject.

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THE LANCET
LONDON: SATURDAY, OCTOBER 19, 1957

The Two-stage Mechanism in Carcinogenesis

THE discovery of the means of inducing tumours at will in animals led naturally to attempts to analyse the processes which precede tumour formation, for it was soon realised that a long latent period usually separated the application of a carcinogen from the emergence of malignant or even of benign tumours. The experiments of DEELMAN [1] were perhaps the first to clarify the processes involved in tumour development. He showed that a crop of papillomas was precipitated along the lines of healing of deep incisions in mouse skin which had previously been tarred. His findings were confirmed in rabbits by MACKENZIE and ROUS.[2] Further work by ROUS and his colleagues, using the chemically induced rabbit papilloma, culminated in the suggestion [3] that "the carcinogen acts in two ways: it changes normal cells into neoplastic cells and encourages the multiplication of these latter." These two actions were termed initiation and promotion. In the same year MOTTRAM [4] showed that a single application of a carcinogen to mouse skin was sufficient to induce or initiate latent tumour cells, which could be demonstrated only by subsequent treatment of the area by a promoting agent. BERENBLUM and SHUBIK [5] obtained quantitative evidence that carcinogenesis consists in an initiating phase, induced by a carcinogen, and a promoting phase, which can be effected by various agents. BERENBLUM [5] regarded the number of tumours produced as a measure of the potency of the initiating process; while the speed with which they appear, or the latent period, depends on the efficacy of the promoting process. The cellular change induced by an initiating substance is irreversible, instantaneous, and invisible. Promotion is a gradual process, reversible in the early stages and finally irreversible.[6] BERENBLUM and SHUBIK also showed that promoting agents can act only on cells which have received an initiating stimulus. Attempts to sensitise cells by means of non-specific substances applied before the carcinogenic treatment did not succeed.

Most chemical carcinogens combine initiating and promoting activity; but on mouse skin urethane acts as a pure initiator, and croton oil as a promoter which also has a slight power to initiate tumour formation. Promoting agents often have irritant properties and elicit continuous reparative hyperplasia. "The simplest explanation for the mechanism of promoting action would be that continued cellular proliferation, of a non-specific character, was responsible for encouraging dormant tumour cells to acquire the properties of a growing tumour." [7] This hypothesis, though attractive, is untenable because many substances which cause epithelial hyperplasia fail to function as promoting agents. Another explanation of promoting action would be that it induces ischæmia of the subepithelial tissues, usually accompanied by fibrosis. Although ORR [8] and others have shown that artificially induced fibrosis augments skin carcinogenesis, not all forms of neoplasia are associated with fibrosis (e.g., certain chemically induced liver tumours) and therefore fibrosis cannot be regarded as an essential part of promotion. Initiation might be regarded as a somatic gene mutation, since it is an instantaneous and specific change. But when BERENBLUM and SHUBIK [5] tested a powerful mutagen—sulphur mustard—for initiating action on mouse skin, the results were negative. Nor is there any clear correlation between the actions of mutagens and carcinogens, though these have much in common.

The work on initiating and promoting factors has been done mostly on skin epidermis. A demonstration of similar mechanisms in other forms of carcinogenesis is therefore of great value. JULL,[9] using an inbred strain of mice in which the breast is unusually susceptible to carcinogenic chemicals, showed that the chemical acted as the initiator and the steroid hormones of the ovary (œstrogen and progesterone) as the promoters of mammary cancer. Extending this work he has found that (as in skin carcinogenesis) if, after a limited application of a carcinogen, treatment with the promoting agent is delayed the resulting tumour incidence is unaffected. This important principle brings home the certainty that in man, even if the initiating phase takes place in childhood, the delayed action of promoters, such as irritants or hormones, will be followed by tumours late in life.

PLATT [10] has suggested that the long latent period in carcinogenesis could be explained by assuming that the carcinogen causes cells to proliferate over a long period at a rate greater than normal. If, further, the chromosomal substance of the affected cells duplicated more and more inaccurately as the number of divisions was increased—a condition which might be envisaged in any ageing cells—and if the nuclear aberration was the cause of the malignant change in the cell, the long latent period would be explained. ARMITAGE and DOLL,[11] after analysing the mortality-rates of cancers in man at certain sites, were inclined to think that carcinogenesis might be a complex process of six or seven stages, but pointed out that there was no direct experimental evidence that tumour production was likely to involve more than two stages. These workers [12] have re-examined mortality data and regard the results as consistent with the theory that cancer is induced in two stages—one or both of which may consist in a somatic mutation. Such arguments must be accepted with reserve. There is no experimental evidence that the first stage in carcinogenesis is a change in the mitotic rate of the cell. In fact,

1. Deelman, H. T., Van Erp, J. P. *Z. Krebsforsch.* 1926, **24**, 86.
2. MacKenzie, I., Rous, P. *J. exp. Med.* 1941, **73**, 391.
3. Friedewald, W. F., Rous, P. *Ibid*, 1944, **80**, 101.
4. Mottram, J. C. *J. Path. Bact.* 1944, **56**, 181.
5. Berenblum, I., Shubik, P. *Brit. J. Cancer*, 1949, **3**, 109.
6. Salaman, M. H., Roe, F. J. C. *Ibid*, 1956, **10**, 79.
7. Berenblum, I. *Advanc. Cancer Res.* 1954, **2**, 158.
8. Orr, J. W. *Brit. med. Bull.* 1947, **4**, 385.
9. Jull, J. W. *J. Path. Bact.* 1954, **68**, 547.
10. Platt, R. *Lancet*, 1955, i, 867.
11. Armitage, P., Doll, R. *Brit. J. Cancer*, 1954, **8**, 1.
12. Doll, R., Armitage, P. *Ibid*, 1957, **11**, 161.

some carcinogens cause necrosis followed by reparation from outside the treated area.[13] There is no evidence that carcinogens cause somatic mutations. The promoting process, though involving reparative or other types of hyperplasia and therefore probably an increased mitotic rate, is manifested only by a limited number of agents causing hyperplasia. Finally, experimental evidence is against the stages in carcinogenesis being limited to two. Two stages—initiation and promotion—have been satisfactorily demonstrated under certain strict experimental conditions, but little account has been taken of the factors concerned in the change from benign to malignant tumours and of the progression of certain dependent tumours to the autonomous state.[14] GREEN'S immunological concept of carcinogenesis[15,16] offers an explanation of all the stages discussed here, from the primary stage of initiation by a carcinogen to the final stage of the fully autonomous tumour cell. These ideas suggest that the change is one of successive loss of cellular characteristics by, for example, protein deletion, the difference between the resultant cancer cell and its normal precursor being the summation of many small changes. Conceivably many factors affect the progress of tumour formation at a number of different points—an idea that is reinforced by the variety of ways in which the disease can proceed in man.

Periureteric Fibrosis

MANY a clinical reputation lies buried behind the peritoneum. In this hinterland of straggling mesenchyme, with its vascular and nervous plexuses, its weird embryonic rests, its shadowy fascial boundaries, the clinician is often left with only his flair and his diagnostic first principles to guide him. Non-specific periureteric fibrosis is likely to tax them both. Of this rare abnormality, first described by ORMOND in 1948,[17] RAPER gave an excellent account [18]; and further cases have been reported.[19,20] Its pathology is baffling in its simplicity. There is progressive fibrosis, spreading laterally from the great midline vessels, gradually engulfing, distorting, and finally strangling both ureters (occasionally only one). The microscopic picture is not unlike that of post-irradiation sclerosis, but cellular activity is more vigorous; and most pathologists could recall instances where an intraperitoneal inflammatory condition, such as diverticulitis or regional enteritis, has provoked a similar reaction. In non-specific periureteric fibrosis, however, no primary cause can be found; and, despite the subacute or chronic inflammatory character of the lesion itself, general symptoms and signs of bacterial invasion are lacking. (One of RAPER'S patients had had a recent episode of acute pleurisy, which had been treated by salicylates; and in the case reported by CHISHOLM et al.[21] there had been a nine-year history of ulcerative colitis.) Cultures and inoculations of biopsy material have been consistently negative; fever is typically absent or late; the erythrocyte-sedimentation rate and white-blood-cell count may be normal; and general ill health is usually delayed until the onset—sudden or gradual—of renal failure. RAPER also stresses the absence of secondary lymph-node enlargement. Malignancy, in the usual sense, can be excluded. Even when the creeping fibrosis completely obstructs the ureters, it does not actually invade them—a point of great therapeutic and prognostic, as well as diagnostic, importance. Moreover, there is evidence that the process, whatever its nature, is self-limiting: in the case reported by MILLER et al.[22] the abdominal mass was still palpable two years after urine-flow had been restored by a fortnight's ureteric catheterisation. On the other hand, the occasional absence in anuric patients of any mechanical block to ascending pyelography is reminiscent of advanced retroperitoneal malignant infiltration. It seems that in both conditions effective peristalsis can be abolished, even though the lumen of the ureters may still be patent. (Peristalsis is, of course, far less likely to be restored by retrograde catheterisation when the obstructive agent is malignant disease.) RAPER has marshalled evidence which suggests that the disease begins as a periarteritis; but only one patient (in whom the disease was unilateral) presented with symptoms of an acute arterial block.

Clinically renal failure marks the climax of an illness which often mimics commoner conditions. At an early stage the symptoms usually point to a growing retroperitoneal lesion; but this limited diagnosis is rarely made. Perhaps we are getting more scientifically minded and less proficient in spotting a purely clinical syndrome. Retroperitoneal pain can be severe and persistent enough to drive the most phlegmatic patient to distraction; but, when there are no abnormal physical findings, his complaint is likely to be received with incredulity, or even hostility. We are secretly annoyed that it does not fit any of the more familiar types; we are affronted by its erratic response to standard sedation; and a succession of negative laboratory tests strains our faith, not in our own judgment, but in the truthfulness of the patient. A helpful diagnostic feature is the "pendulum" character of the pain—because it is essentially caused by pressure on relatively fixed and highly sensitive structures, it is strongly influenced by gravity. Commonly the patient prefers to lie with his face down; and the astute clinician may diagnose, often in the face of contrary evidence, an expanding retroperitoneal lesion from watching the patient, when off his guard, buckling over the edge of his bed. The pattern of these contortions gradually changes as the lesion expands; and they rarely afford such complete relief as they often do from pain caused by a diaphragmatic hernia or a high gastric ulcer.

Radiographic investigations, at any rate in the early phases, more often mislead than clarify. The obligate barium series may be entirely negative or, worse, may provide the clinician with a wide choice of red herrings. (Of the few reported cases of non-specific periureteric fibrosis, at least two had unrelated but bona-fide peptic ulcers.[18,20]) Pyelograms often show distortion of one or both ureters and the signs of renal

13. Orr, J. W. *Ibid*, 1955, **9**, 623.
14. Foulds, L. *Cancer Res.* 1954, **14**, 327.
15. Green, H. N. *Brit. med. J.* 1954, **ii**, 1374.
16. Green, H. N., Wakefield, J., Littlewood, G. *Ibid*, Oct. 5, 1957, p. 779.
17. Ormond, J. K. *J. Urol.* 1948, **59**, 1072.
18. Raper, F. P. *Proc. R. Soc. Med.* 1955, **48**, 736.
19. Case Records of the Massachusetts General Hospital. *New Engl. J. Med.* 1956, **255**, 90.
20. Case Records of the Massachusetts General Hospital. *Ibid*, 1957, **256**, 1198.
21. Chisholm, E., Hutch, J. A., Bolomey, A. *J. Urol.* 1954, **72**, 812.
22. Miller, J. M., Lipin, R. J., Meisel, H. J., Long, P. H. *Ibid*, 1952, **68**, 447.

back-pressure; but, though this knowledge is valuable, it rarely sheds light on the nature of the lesion. In a recently reported case,[20] radiographs of the lumbar spine showed narrowing of the intervertebral space between the fourth and fifth lumbar vertebræ, vertical striations in the body of the fourth vertebra, and mild diffuse demineralisation of the skeleton. Later, none of these findings proved significant; but by then the patient had undergone a course of irradiation to his spine (for a supposed intraosseous angioma); hæmangiosarcoma had to be seriously considered in the preoperative differential diagnosis; and the demineralisation suggested a number of malignant tumours of which hypercalcæmia and hypercalcuria is an occasional feature. Retroperitoneal gas insufflation may be considered [21]: there is no doubt that in some of the most perplexing cases it can provide information unobtainable by other means. But, despite all precautions, this investigation still carries an appreciable mortality—higher, in fact, than the "basic" mortality of laparotomy—and, in its present forms, it is rapidly falling into well-merited disrepute.

Several cases show that an exploratory operation is not necessarily the answer to the clinician's prayer. A patient discussed at the Massachusetts General Hospital [20] gave a four-month history of left-sided abdominal pain and of loss of weight; but there were few abnormal physical findings, and the radiographic and laboratory investigations were inconclusive. At laparotomy a poorly defined mass was found behind the pancreas, extending over the lumbar vertebræ; and biopsy (the specimen was taken with misgiving because of the proximity of the inferior vena cava) showed "subacute and chronic inflammation with fibrosis." This report was interpreted by one of the surgeons as showing that the biopsy material had been taken from the periphery of the lesion; and he believed that the severity of the symptoms indicated "a great deal of activity in the tumour, probably necrosis, which could explain the surrounding inflammatory reaction." The doctors in charge, however, were struck by similarities in the clinical and pathological picture between this and another patient who had been seen at the same hospital a year previously.[19] The first patient, also an elderly man, had been operated on after a few months' history of abdominal "soreness" and the sudden onset of anuria; and at operation bilateral ureteric obstruction, caused by "a peculiar retroperitoneal inflammatory fibrotic process," had been found. The similarity was confirmed at reoperation on the second patient, when the obstructed ureter was freed from its dense fibrous envelope and several further biopsy specimens were taken. The patient did well postoperatively. The prognosis, if relief from obstruction is not too long delayed, appears to be fair.

Biopsy must obviously play a crucial part in the diagnosis, management, and prognosis of this condition; but all retroperitoneal lesions remind us that what is indefinite and difficult to fit into a single pattern clinically is not likely to be less indefinite or more typical when magnified a thousandfold. The error in the biopsy interpretation recorded in the Massachusetts General Hospital case [20] is the reverse of the classical mistake: far more commonly (and usually with more serious results) the biopsy specimen is taken as a representative sample of the whole lesion, when in fact it is not. A great deal of misunderstanding and false prognostication could be avoided if the microscopic appearance of the lesion was regarded as just one valuable sign—neither more nor less valuable than others elicited by the unaided senses. Diagnosis of retroperitoneal disease provides ample scope for *la grande synthèse*; but what used to be the final measure of the diagnostic acumen of the single clinician is today the far more stringent test of the combined skill of a whole team.

21. Landes, R. R., Ransom, C.L. *Surg. Gynec. Obstet.* 1957, **105**, 268.

Mussels

THOSE who eat mussels run four apparently separate risks: (1) "musselling," which appears to be an allergic response to some part of the mollusc; (2) an uncommon, though sometimes fatal, paralytic disease due to an alkaloid produced by a free-living protozoon ingested by the mussels; (3) enteric fever (but mussels seem less blameworthy than oysters, probably because they are usually eaten cooked); (4) gastroenteritis caused by a heat-stable toxin. The incidence of musselling is unknown, but the sufferer seldom risks his affliction a second time. No example of paralytic mussel poisoning seems to have been reported for a long time. The incidence of enteric fever due to shellfish as a whole has been much reduced by the ingenious technique by which they are made to clear themselves of fæcal bacteria by a short sojourn in clean water. Gastroenteritis ensues occasionally; but an investigation of its cause is seldom possible, and for this reason an account by GEMMILL[1] of the disease in Glasgow since 1950 is welcome.

There are not many mussel vendors in Glasgow, and their shops are clean and orderly. They draw their supplies from Loch Long and the Gareloch, both of which receive a certain amount of raw sewage. 28 people in 1950 and 49 in 1953 were stricken with gastroenteritis after a dish of mussels; and the fact that their ages ranged from 2 to 76 throws an interesting light on dietary habits. These were not explosive outbreaks but spread over several weeks, and those affected were only a small proportion of those who had eaten mussels in Glasgow. Since the mussels had been cooked for an hour or more, and since the chance of reinfection after cooking was slight, it is not surprising that no pathogenic bacteria were found in them or in the fæces of the patients. The short incubation period (1–17 hours) and rapid recovery both suggested that the disease was due to the ingestion of a pre-formed toxin. GEMMILL suggests that this disease is associated with a toxin formed—presumably in vivo—by bacteria of fæcal origin, but the evidence for this is insufficient. Some fæcal bacteria are to be found in the water of almost every mussel bed, and consequently in almost every mussel. With allowances for the errors inherent in counting methods, there was no clearcut difference between the total bacterial count of suspect and of other mussels. All other examples of enteritis due to a pre-formed bacterial toxin arise when the infected food has been kept for some hours at a temperature which allows bacterial multiplication—a condition that can seldom prevail in these sea lochs.

That certain fishes are poisonous at all times or at certain seasons is an old story not always confirmed.

1. Gemmill, J. S. *Med. Offr*, 1957, **98**, 111.

Reports are fascinating but contradictory. Some illnesses which follow a meal of sea food are due to frank bacterial infection, inherent in molluscs or acquired in the process of "cleaning" fish. Some are instances of botulism. In some fish the noxious properties appear to be limited to the reproductive organs, and in Ireland pike are thought to be unwholesome in their breeding season. Scattered through the literature are fairly numerous accounts of poisoning by alkaloid-like substances which may or may not survive cooking. Some of these are neurotoxins, and of these the one which has received most attention is that associated with "mussel poisoning" on the Pacific coast of North America. SOMMER and MEYER[2] showed that this extremely toxic compound is produced, not by the mussel, but by a specific dinoflagellate which the mussel ingests. Like many other members of the phytoplankton this enjoys transient seasons of local superabundance which coincide with outbreaks of paralytic disease among mussel eaters. Similar small creatures have been suspected of toxigenic properties in other places, and the diseases attributed to them have not been all of one kind. With this example in mind it is a pity that a marine biologist was not added to the team which investigated the mussel poisoning in Glasgow. He might have added nothing to our knowledge, but it cannot be said that in this instance the classical methods of epidemiology have been illuminating.

Annotations

STRESS PROBLEMS IN GENERAL PRACTICE

STRESS was the theme of a weekend conference in London on Oct. 5 and 6, arranged jointly by the Metropolitan and Home Counties faculties of the College of General Practitioners and the Society for Psychosomatic Research. Dr. Desmond O'Neill's definition of a stress disorder was accepted, but subsequent discussion emphasised the difficulty of confining emotions, ideas, and sensations within the limits of close definition. That stress is a two-way affair, affecting the doctor as well as his patient, was noted by Dr. R. R. Bomford, whose quotation from one of his surgical teachers came as balm in Gilead: "You cannot be expected," he said, "to reach a complete and final solution to every conceivable problem in every conceivable situation, as many doctors feel they ought. You can only be expected to do your best with the facts available at the time, and the particular degree of knowledge and experience which you have."

Regarding treatment, it was agreed that listening to the patient was important; history-taking, besides contributing to the accuracy of diagnosis, enabled the patient to release his pent-up emotional tension, and was a form of therapy. Dr. Philip Hopkins recommended special appointments for longer sessions than can be fitted into the routine of surgery consultations. Dr. S. Barton Hall compared the scope of treatment of stress disorders which was offered by general and by hospital practice and suggested that "modified insight therapy" be applied in general practice. Dr. Sidney Abrahams analysed the relation of the doctor to the patient with a stress disorder. Continuity of care should characterise the relationship, and also continuity of responsibility to keep the patient satisfactorily adjusted to his physical and emotional environment.

The conference approached research into psychosomatic disorders from two angles—that of the hospital research-worker and that of the general practitioner. Dr. John Hambling described the use of somatic indicators of emotional states, in particular the blood-pressure, as well as skin temperature, blood-flow, muscle tension, and salivary secretion. Great care was needed in interpreting results. The psychoanalytic method had its place, but advances in our knowledge of stress disorders might come from biology, epidemiology, and sociology. The family doctor's unique opportunity to observe the natural history of stress disorders was described by Dr. C. A. H. Watts. He could take advantage of continuous care to observe continuously; and the general practitioner who observed and recorded and was self-critical had a testing-ground of diagnosis more accurate than any other—except perhaps the postmortem room. Dr. Watts' comment on the lack of objective measurements in general practice was taken up in the subsequent discussion, in which it was observed that a large body of informed opinion could lead to valid conclusions even in the absence of statistics.

CEREBRAL EMBOLISM

STELLATE-GANGLION block and the administration of anticoagulant drugs have been advocated for the immediate treatment of cerebral thrombosis and embolism. Barham Carter[1] has made a valuable controlled study of these methods in cerebral embolism. In four years 575 patients with hemiplegia of sudden onset were admitted to Ashford Hospital, Middlesex, and of these 60 were thought to have had a cerebral embolism. The diagnosis was made on the very sudden appearance of hemiplegia, hemianopia, or aphasia in a patient who had auricular fibrillation, subacute bacterial endocarditis, recent coronary thrombosis, or mitral stenosis without fibrillation, and whose cerebrospinal fluid contained no blood. Mitral stenosis complicated by auricular fibrillation accounted for more than half the cases. A different method of treatment was given to these patients (all under the age of 70) in each of the four years, while nursing care and "accessory methods of treatment" were not altered. In 1952 (16 patients) unilateral stellate block with 1% lignocaine was repeated daily for ten days. In 1953 (18 patients) no specific treatment was given. In 1954 (15 patients) a single stellate block was done on admission (usually within twenty-four hours of the embolism and often within twelve hours); six hours later heparin was given intravenously followed by two intramuscular injections at six-hour intervals; oral anticoagulant therapy (phenindione) was started with the first dose of heparin and continued for a fortnight. The aim was to keep the prothrombin level between 10 and 30% of the normal. In 1955 (11 cases) anticoagulant treatment was given as in the previous year, but no stellate block was done.

There has been much discussion as to whether anticoagulant drugs should be given in cerebral thrombosis and embolism, and, in general, opinion[2–4] in this country has been against their use. One reason for this is that it is often hard to distinguish cerebral thrombosis from cerebral hæmorrhage, and the absence of blood from the cerebrospinal fluid does not absolutely exclude hæmorrhage: Rose,[5] in a survey of 205 fatal cases of cerebral hæmorrhage, found no blood in the subarachnoid spine at necropsy in 10%. Another reason for not using anticoagulants is the occurrence a few days after cerebral infarction of secondary cerebral hæmorrhage due to alteration in the nutrition of an arterial wall in relation to the area of softening; and Rose, in his series of 205 cases, concluded from pathological examination that this had happened in 30. In Barham Carter's series death was accelerated by anticoagulant treatment in

2. Sommer, H., Meyer, K. F. *Arch. Path. (Lab. Med.)* 1937, **24**, 560.

1. Carter, A. B. *Quart. J. Med.* 1957, **26**, 335.
2. Symonds, C. P. *Practitioner*, 1956, **176**, 130.
3. Brain, W. R. *Lancet*, 1954, ii, 831.
4. Ellington, J. St. C. *Brit. med. J.* 1955, ii, 1199.
5. Rose, W. McI. *Lancet*, 1948, ii, 561.

1 case—that of a woman aged 68 in whom, on the sixth day of treatment, the prothrombin-time suddenly rose to sixty seconds, and, despite discontinuation of treatment, continued to rise. Hæmaturia developed and she died in uræmia, necropsy showing extensive bleeding into the kidneys. After this, patients over the age of 60 were given a reduced dose of anticoagulant drugs.

Each case was finally assessed three months after the occurrence of embolism. The patients were divided into four groups—recovered, improved, not improved, and died. By recovery was meant a return to normal life with full work and no or minimal disability, though there might be some impairment of fine movements of the hand. In the improved group were patients in whom some useful movement was possible at the elbow and wrist. There was no appreciable difference in the results between the 1952 patients who were treated by repeated stellate-ganglion block and the 1953 group to whom no specific treatment was given; and results were very similar in the group treated by anticoagulant drugs alone and in that where anticoagulant treatment was preceded by a single stellate block. But on comparison of patients who had received anticoagulants, with or without a single stellate block, with those who had not had either of these treatments the former were found to have fared definitely better.

Barham Carter's results show that stellate-ganglion block has not been of value in the early treatment of cerebral embolism, but suggest that anticoagulants may be helpful.

INTRAVASCULAR CARBON DIOXIDE FOR ANGIOGRAPHY

SUCH organic iodine compounds as diodone and sodium acetrizoate are in universal use as contrast media for all forms of angiography, but because they occasionally produce toxic reactions they are not completely satisfactory. Air and oxygen, which have a lower radio-opacity than soft tissue, are extensively used to provide contrast for examinations, including encephalography and pre-sacral insufflation; but they cannot be used intravenously because of the danger of embolism. Carbon dioxide is twenty times more soluble in serum than oxygen, and possibly might be injected intravenously without the same risk. Durant et al.[1] have injected intravenously in dogs carbon dioxide in amounts as large as 7·5 ml. per kg. body-weight. With doses of this order there was a brief rise of 5-10 vols. % of carbon dioxide in the whole blood, with a brief period of hyperpnœa. The change in blood-gas content was greatest within half a minute, and the content was normal again in one to two minutes. The blood pH was little altered, and ventricular pressures changed surprisingly little. The same amount of carbon dioxide was injected into the left ventricle, the carotid artery, and the aorta in dogs, with little clinical disturbance and apparently no residual sequelæ. Encouraged by these experiments Durant et al. have used carbon dioxide to outline the cardiac chambers in man, the first subjects being anencephalic fœtuses. So far the gas has been given only into systemic veins, and any patient who might have an intracardiac shunt has been excluded. Injections of 50–100 ml. have been made without accident, but a dose of 2 ml. per kg. has not been exceeded. Such volumes of gas displayed the right heart quite well, but contrast was less sharp than with iodine compounds. Durant et al. emphasise the importance of using absolutely pure carbon dioxide, and of perfusing the apparatus to expel all traces of air.

This may prove to be a valuable technique if experience confirms its safety even in the presence of intracardiac shunts and shows that it can give at least as much detail as the more usual contrast agents.

1. Durant, T. M., Stauffer, H. M., Oppenheimer, M. J., Paul, R. E. *Ann. intern. Med.* 1957, **47**, 191.

PEPSINOGEN IN URINE AND BLOOD

THE presence in urine of a proteolytic enzyme active in strongly acid solution has been known for nearly a century.[1 2] The term "uropepsinogen" has usually been applied to the inactive form which is excreted, "uropepsin" being formed from this at a strongly acid reaction. The claim that uropepsinogen excretion quantitatively reflects gastric pepsin output[3] has been strengthened by the observation that uropepsinogen "disappears after total gastrectomy, is low or absent in pernicious anæmia, tends to be elevated in duodenal ulcer, and falls after partial gastrectomy."[4] According to Sircus,[5] "the measurement of the excretion of uropepsinogen has the advantage [over test meals] of providing a readily repeatable quantitative estimation of peptic cell function with the minimum of disturbance to the patient, and without the aid of artificial stimuli."

In recent years, however, most workers have followed Mirsky et al.[6 7] in paying more attention to plasma-pepsinogen levels, on the ground that these vary less from day to day and from hour to hour under normal conditions,[4 7 8] and therefore reflect more accurately differences in gastric secretion. The relation of plasma levels to gastric disorders has been shown to be essentially the same as that for urinary levels. Using either fluid, there is much overlap between the ranges of levels found in healthy people and those in patients with various diseases. But at the extremes some patients with peptic (particularly duodenal) ulcer have pepsinogen levels above the ranges found in association with carcinoma of the stomach,[2 4 5 9] whereas a low level in a case of peptic ulceration raises a suspicion of malignancy. Pernicious anæmia is accompanied by a low plasma-pepsinogen (in fact, probably none at all when correction is made for the non-specificity of the method[7 10]), and little or no uropepsinogen excretion.[2 5] High pepsinogen levels accompanying gastro-intestinal hæmorrhage indicate a duodenal ulcer as the site, lower levels being found when the blood comes from œsophageal varices associated with hepatic cirrhosis.[2 5 9] In these and other conditions estimations of pepsinogen have appeared to hold out hopes of clinical usefulness. But the work of Hirschowitz et al. in Michigan has necessitated complete revision of ideas on the relation of these levels to gastric pepsin output. During research on the effects of corticotrophin and cortical steroids, they have shown that the renal clearance of pepsinogen can vary much under hormonal control without changes in blood-levels.[11 12] Furthermore, one of their subjects, in whom an acute prepyloric ulcer developed after an intravenous infusion of corticotrophin, had much increased plasma and urine pepsinogen levels for many months afterwards, while his gastric pepsin secretion was very low.[12] They remark that "the reasons for the lack of correlation between gastric pepsin and urinary pepsinogen lie in the complex and ill-understood factors which govern the discharge of the enzyme from the gastric cells into the blood and in the secondary factors which determine the amount of enzyme cleared from the blood by the kidney."[11] Thus it appears that the picture of gastric pepsin output is reflected with a

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6. Mirsky, I. A., Futterman, P., Kaplan, S., Broh-Kahn, R. H. *J. Lab. clin. Med.* 1952, **40**, 17.
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10. Hirschowitz, B. I. *J. Lab. clin. Med.* 1955, **46**, 568.
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variable degree of distortion in the blood, and that the image is liable to become even more blurred by passage through the kidneys. When what Hirschowitz calls "the peptic potential" of the stomach is high, the blood and urine pepsinogen levels are likely to be greater than normal. Where the stomach has been removed, or where it is inactive as in pernicious anæmia, pepsinogen of gastric origin will not be found in blood or urine. Between these extremes, little useful differentiation of clinical conditions can be expected.

This is not the end of the pepsinogen story. There are many unanswered questions. Is all blood and urine pepsinogen of gastric origin? What is the significance of Hirschowitz's finding [13] of relatively large amounts of pepsinogen in leucocytes? Is it true that adrenal cortical function can be assayed by the response of the plasma-pepsinogen level to an injection of corticotrophin [8]; and if so, why? Does the increase of renal pepsinogen clearance in response to corticotrophin, demonstrated by the Michigan workers, depend similarly on normal activity of the adrenal cortex? Is it true that "duodenal ulcer develops only in those with high serum pepsinogen concentrations"? In the paper in which this claim is made,[14] Weiner et al. report a certain amount of success in psychiatric differentiation between subjects with high and low serum-pepsinogen levels. They assume that these levels are an index of gastric pepsin secretion. In view of the Michigan reports, however, this may not be a valid assumption especially in the group of patients in whom they demonstrated persistent mental conflicts. May it not be that the high pepsinogen levels are in fact manifestations of those conflicts, resulting from pituitary-adrenal changes and not necessarily related to gastric pepsin secretion in any simple way? Have we here possibly a glimpse of some part of the unknown pathway from the mind via the endocrine system to the gastric mucosa? It is a fascinating speculation.

TUBERCULOSIS IN THE SCHOOL

UNFORTUNATELY we have not yet reached, in this country, the attitude to the prevention of tuberculosis whereby a new case calls into play a shock brigade to find, isolate, and treat the source case. But when tuberculosis is detected in a child, and especially in a child of school age, quick and decisive action should be possible. Moss and Fairweather [15] have shown in Clitheroe how rewarding can be the search in a school for fresh cases.

A four-year-old boy had a pleural effusion, and three months later tuberculous meningitis developed in another boy of the same age. No source of infection was found until a year-old boy died of tuberculous meningitis three months later. He had been infected by a woman who had frequently visited the home. The two four-year-old children were linked with this woman because she served the meals in their school. She had been taken on as a temporary worker without any sort of medical examination, and when her health had begun to fail after "influenza," sixteen months previously, she had not followed the suggestions of the staff to go and see her doctor.

A mass X-ray unit quickly visited the school, and 339 (85%) of the 400 children and all the teachers and domestic staff were examined. 2 children were found to have active pulmonary tuberculosis and 3 were kept under observation. Other cases were discovered through the general practitioners and hospitals—2 of erythema nodosum, 2 of pleural effusion, and 3 of active primary lung lesions. In all, 15 new cases were found; and all these patients, except the one-year-old child who died, had had dinner at school. A tuberculin survey, using the jelly test, showed that 86 children (21·9%) had positive reactions, but there were some equivocal results and therefore a Mantoux test with 0·005 mg. P.P.D. was performed on all except the definite positives. It was found that of 408 pupils 131 were positive; 11 with doubtful jelly tests may have been positive, but the Mantoux test could not be carried out and thus the percentage positive was about 35. An age-distribution curve showed a bulge in the 5–8-year-old group. (A similar bulge does not appear in curves from other recent surveys, such as the Rhondda Fach,[16] where the Mantoux-positive rate was 24%, and the Calder Valley,[17] where it was 39%.) The known cases in the bulge numbered 13; but even when this total is subtracted the line still does not come down to the other lines, and Moss and Fairweather therefore postulated that probably a further 17 pupils were infected, giving a total of about 30.

All positive reactors not already under medical care had new films taken about nine months after the open case was discovered, and 30 pupils showed either enlarged hilar glands or a primary focus, or both: to this total must be added the 13 children already known to have chest lesions, making 31·5% of positive reactors. B.C.G. vaccination was offered to the Mantoux-negative 13-year-olds, and all accepted.

Nowadays, in some areas when a schoolchild is found to have a positive Mantoux reaction the whole school is tuberculin-tested by the Heaf method; the positive reactors are X-rayed and their family background is investigated. The Heaf test is sufficiently reliable for such studies, and it is simple and does not frighten the child. The parents of all Mantoux-negative children should be offered B.C.G. vaccination. Every effort must be made to X-ray all the adults associated with a school from the stoker to the school-bus driver, from the student teacher to the headmaster. In urban areas where the milk is likely to have been pasteurised, a straight X-ray of the abdomen is usually unnecessary, but in rural areas such an X-ray can be of considerable value. The undoubted worth of routine Heaf-gun testing at school medical examinations has not been realised: assessing the Mantoux state of young people will not only lead to the detection of open cases among them but also indicate the level of open active tuberculosis in the adult population.

ACTA VIROLOGICA

VIRUS research had its origins in Europe: Jenner and vaccinia, Pasteur and rabies; the first demonstration of the filterability of an animal virus in Löffler and Frosch's work on foot-and-mouth disease. In the past three decades American work has come to the fore; and among notable contributors of many other nationalities British and Australian workers have been prominent. It is not surprising therefore that English has become the accepted international language for virology. To the two journals already devoted exclusively to virus research, a third has now been added, *Acta Virologica*, the first issue of which has just been received in this country. It is published in Prague under the auspices of the Czechoslovak Academy of Science, and simultaneous versions in English and Russian are to appear quarterly.[18] In their introduction the editors, Dr. D. Blaskovic, of Bratislava, and Dr. A. A. Smorodintseff, of Leningrad, express the hope (which will be widely echoed) that the new venture will help to promote international understanding and cooperation. To assist them, they have an editorial board which includes many distinguished virologists from Eastern Europe.

The success and value of the journal will ultimately be determined by the quality of the material it can attract. In the first issue the standard varies, but it can hardly be otherwise until the journal has begun to make itself more widely known. The translation has been done very efficiently and the editors deserve warm praise for giving their fine idea so successful a start.

Prof. ANDREW CLAYE has been elected president of the Royal College of Obstetricians and Gynæcologists.

14. Weiner, H., Thaler, M., Reiser, M. F., Mirsky, I. A. *Psychosomat. Med.* 1957, 19, 1.
15. Moss, P. D., Fairweather, J. H. *Brit. J. Tuberc.* 1957, 51, 258.
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17. Keidan, S., Lyons, J., Mann, B., Willthew, G. A. *Ibid*, 1952, i, 1390.
18. The annual subscription is 30 kčs. Orders may be sent to ARTIA, 30, Ve smečkách, Prague 2, POB 790, Czechoslovakia.

Special Articles

FATALITY FROM THREE COMMON SURGICAL CONDITIONS IN TEACHING AND NON-TEACHING HOSPITALS

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IN the course of some studies of appendicitis, we became interested in estimating the number of admissions to hospital each year for this condition. We therefore turned to the published report of the hospital inpatient inquiry, and it can be inferred from the samples on which this study was based that the number of cases of appendicitis treated in hospital in England and Wales in 1951 was probably in the region of 120,000. During that year there were close on 1200 deaths certified to appendicitis. The hospital inpatient data are given separately for teaching and non-teaching hospitals, and we were surprised to find, on doing the sums, that the case-fatality was much higher in the non-teaching hospitals. The sample of teaching hospitals reported 7139 cases of appendicitis with 43 deaths (a case-fatality of 1 in 166), while the sample of non-teaching hospitals reported 2795 cases with 38 deaths (a case-fatality of 1 in 74).

The rest of the published data (General Register Office 1955) were then examined to see if differences also occurred in other diseases. For differences in case-fatality to be demonstrable from this material the disease must be common and it must have an appreciable mortality. It was impossible to use any data on malignant disease, for in both types of hospital some of the admissions will be for radical treatment and others for terminal care. Eventually, three conditions were selected for more detailed study—appendicitis, perforated peptic ulcer, and hyperplasia of the prostate. For each of these there were large numbers of cases, and the published data referred to a single clinical entity or, at least, to a group of closely related conditions. The main case-fatalities in 1951 for the two types of hospital are set out in table I. Further details are given later and the general picture in 1951 is described in appendix I.

The implications of the comparisons in table I seemed sufficiently important to make further inquiries necessary. From 1949 to 1951 the General Register Office (G.R.O.) collected data about the patients discharged from selected hospitals, and these have now mostly been published. In 1953 and 1954 a further collection of information was made from a different sample of hospitals which has not been published. Following our analysis of the 1951 material we approached the G.R.O., who kindly transcribed for us some of the data they had collected in 1953–54.[1] In the more detailed analyses that follow, the 1953–54 figures are given alongside those of 1951.

Materials and Methods

Until 1952 the G.R.O. inquiry was made on the basis of the collection of reports of all patients discharged from about 50% of the teaching-hospital beds, and from a group of non-teaching hospitals whose beds formed about 3% of the total non-teaching-hospital beds (excluding mental hospitals) in the National Health Service in England and Wales. The 1953–54 material was different, being based on the records of an effectively random *10%* sample of the patients discharged from about the same proportion as before (50%) of teaching hospital beds, and on a similar *10%* sample of those discharged from non-teaching hospitals containing now about 17% of the beds in this type of hospital in the service.

In one respect this later information (1953–54) is of less use for our purposes, since the numbers of cases reported by the teaching hospitals under the system of 10% sampling are small. In another way, however, these data are a valuable supplement. The non-teaching hospitals in the 1951 inquiry were few, mostly large, and drawn from only five regions. In the 1953–54 inquiry many complete hospital groups and nearly all of the regions were included. All types of hospital—large, middling, and small, ex-voluntary and ex-local-authority—are represented in the sample of non-teaching hospitals, and there is evidence that the data give a representative picture of these hospitals in England and Wales. Features of the data found in both periods are probably not due to selection of particular hospitals or areas. However, in any sample (and particularly in small samples) in which participation by the hospitals was voluntary, the decision that the material is sufficiently representative to justify analysis becomes a matter of common sense and of knowledge of the particular situation. We are not anxious on this score. There is nothing to suggest that, taken together, the non-teaching hospitals included in either the 1951 or the 1953–54 samples were inferior to the average of non-teaching hospitals—or that the teaching hospitals were superior to the average teaching hospital.[2]

TABLE I—NUMBER OF CASES OF CERTAIN DISEASES, NUMBER OF DEATHS, AND CASE-FATALITIES AMONG PATIENTS ADMITTED TO TEACHING AND NON-TEACHING HOSPITALS, 1951

Diagnosis	T.H.*		Non-T.H.*	
	Cases (and deaths)	Case-fatality (%)	Cases (and deaths)	Case-fatality (%)
Acute appendicitis with peritonitis: males, all ages ..	469 (16)	3·4	219 (15)	6·8
Acute appendicitis with peritonitis: females, all ages	360 (15)	4·2	171 (14)	8·2
Perforated peptic ulcer: males, ages 45–64 † ..	393 (30)	7·6	132 (14)	10·6
Hyperplasia of prostate: ages 65–74	660 (41)	6·2	280 (48)	17·1

Throughout the tables, only deaths in hospital are included.
All figures given for 1951 are derived from a sample of the hospitals of England and Wales, containing 50% of the beds in teaching hospitals, and 3% of the beds in non-teaching hospitals (G.R.O. 1955).
* The abbreviations T.H. and Non-T.H. are used for teaching hospitals and non-teaching hospitals throughout these tables.
† The figures given here for 1951 are not exactly the same as those published by the General Register Office because cases of perforated anastomatic ulcer have been added to make them comparable with the data for 1953–54.

Differences in case-fatality might be produced by differences in the patients coming to the two types of hospital, by differences in the severity of their disease, and by differences in the treatment they were given in hospital. The age of the patients affects their experience to a very large extent. Thus, taking both types of hospital in 1953–54 together, 1 in 20 men aged between

1. We understand that copies of the data are available from the General Register Office on repayment.

2. If the deaths in the 1953–54 sample of hospitals are scaled up by the ratio of the number of surgical discharges in the sample to that in the whole country, this gives an "expected" figure for deaths in hospital in the whole country. This expected figure for appendicitis and for perforated peptic ulcer is close to the actual figure, and it is substantially less than the actual figure for hyperplasia of the prostate (G.R.O. 1956a). This does not suggest that the hospitals included in the sample are below the average efficiency.
The distribution of hospitals in 1953–54 by their size (no. of beds) is similar to that of the country as a whole, although the sample included a rather high proportion of the larger hospitals.

TABLE II—NUMBER OF CASES OF APPENDICITIS AT ALL AGES, NUMBER OF DEATHS, AND CASE-FATALITIES * IN TEACHING AND NON-TEACHING HOSPITALS, BY SEX AND DISEASE CATEGORY

Category of appendicitis	1951				1953–54 †			
	T.H.		Non-T.H.		T.H.		Non-T.H.	
	Cases (and deaths)	Case-fatality (%)	Cases (and deaths)	Case-fatality (%)	Cases (and deaths)	Case-fatality (%)	Cases (and deaths)	Case-fatality (%)
Males:								
Acute without mention of peritonitis	1996 (8)	0·4	899 (5)	0·6	366 (1)	*0·3*	997 (4)	*0·4*
Acute with peritonitis	469 (16)	3·4	219 (15)	6·8	77 (2)	*2·6*	190 (13)	6·8
Unqualified ‡	474 (0)	*0*	196 (2)	*1·0*	87 (0)	*0*	486 (2)	*0·4*
Other	439 (0)	*0*	103 (0)	*0*	52 (0)	*0*	123 (0)	*0*
All	3378 (24)	0·7	1417 (22)	1·6	582 (3)	*0·5*	1796 (19)	1·1
Females:								
Acute without mention of peritonitis	1862 (1)	*0·1*	803 (2)	*0·2*	364 (0)	*0*	986 (2)	*0·2*
Acute with peritonitis	360 (15)	4·2	171 (14)	8·2	53 (0)	*0*	159 (6)	3·8
Unqualified	689 (2)	*0·3*	231 (0)	*0*	109 (0)	*0*	735 (0)	*0*
Other	850 (1)	*0·1*	173 (0)	*0*	128 (0)	*0*	184 (0)	*0*
All	3761 (19)	0·5	1378 (16)	1·2	654 (0)	*0*	2064 (8)	0·4

* Throughout this paper case-fatalities based on 5 or more deaths are printed in roman type, those on fewer than 5 in *italic*. The summary rates at the foot of columns are not "standardised" for age.

† The figures given for 1953–54 are derived from a 10% sample of the patients in hospitals of England and Wales containing 50% of the beds in teaching hospitals, and 17% of the beds in non-teaching hospitals.

‡ In both periods the proportion of cases for which the non-teaching hospitals gave insufficient information for the category of appendicitis to be decided was higher than in the teaching, but it seems unlikely that this reflects any important clinical differences.

15 and 64 suffering from appendicitis with peritonitis died, while 1 in 4 such men aged more than 65 died. In the three conditions discussed later in detail, the teaching-hospital patients were on the average younger. For better comparison of the rates in the two kinds of hospital, fatality-rates in narrow age-groups—e.g., 55–64, 65–69—can be used, and examples of this are given in the tables. For rates summarising the experience of the two different types of hospital it is necessary to "standardise" those of the non-teaching hospitals by calculating rates for the non-teaching hospitals at different ages, and applying these rates to a "population" of the same age composition as the teaching-hospital patients. Such "standardised" or "age-adjusted" rates for the non-teaching hospitals can then be compared with the teaching-hospital rates. It was found, however, that "standardisation" had little effect on the differences already found between the two kinds of hospital. Examples are given later.

In the 1953–54 material the cases were divided by type of admission into "immediate" and "other." We do not know what proportion of the "immediate" admissions to either type of hospital were emergencies requiring urgent treatment to save life. It is possible that the non-teaching hospitals, with their lower bed-occupancy (Ministry of Health 1956a), will include more of the less severely ill among their "immediate" admissions. For two of the diagnoses—appendicitis with peritonitis and perforated peptic ulcer—the great majority of the admissions were "immediate," and the division of admissions in this way is of little importance. But there were many admissions for hyperplasia of the prostate that were not "immediate," and since the case-fatality was higher in the "immediate" cases and the proportion of such cases differed in teaching and non-teaching hospitals, this factor has also been allowed for in standardisation. Again, however, this has little effect on the differences already found between the hospitals by simple arithmetic.

TABLE III—NUMBER AND PERCENTAGE DISTRIBUTION OF CASES OF APPENDICITIS IN DIFFERENT AGE-GROUPS, ALSO PERCENTAGES IN EACH AGE-GROUP REPORTED AS HAVING PERITONITIS, IN TEACHING AND NON-TEACHING HOSPITALS: MALES, 1953–54

Age (yr.)	No. of cases in each age-group		% of cases in each age-group		% of cases in each age-group with peritonitis	
	T.H.	Non-T.H.	T.H.	Non-T.H.	T.H.	Non-T.H.
< 5	25	38	5	3	40	18
5–	133	399	28	27	16	9
15–	108	342	22	24	10	9
25–	111	270	23	19	5	7
35–	46	161	10	11	20	15
45–	38	195	8	13	16	22
65+	18	47	4	3	33	36
Not stated	...	1	...	...	...	...
All ages	479	1453	100	100	14	12

"Immediate" admissions only (these form 92% of all admissions with peritonitis).

The age-distribution of cases of all types is similar in the two types of hospital, in either sex, in either period of observation, and whether all admissions or only "immediate" ones are considered. As an example the age-distribution of male patients in 1953–54 is given in table III.

TABLE IV—NUMBER OF CASES OF ACUTE APPENDICITIS WITH PERITONITIS, NUMBER OF DEATHS, AND CASE-FATALITIES, IN TEACHING AND NON-TEACHING HOSPITALS, BY AGE OF PATIENT: MALES, 1951 AND 1953–54 DATA AMALGAMATED

Age (yr.)	T.H.		Non-T.H.	
	Cases (and deaths)	Case-fatality (%)	Cases (and deaths)	Case-fatality (%)
< 15	181 (3)	*1·7*	131 (6)	4·6
15–	317 (8)	2·5	242 (11)	4·5
65+	43 (7)	16·3	35 (11)	31·4
Not stated	5	...	1	...
All ages	546 (18)	3·3	409 (28)	6·8

Case-fatalities based on 5 or more deaths have been given in the tables in roman type and those on fewer than 5 deaths in *italic*.

Appendicitis

When hospitals notify cases of appendicitis to the G.R.O., these are classified according to the International Statistical Classification of Diseases, Injuries, and Causes of Death (World Health Organisation 1948). There are four categories for appendicitis, numbered and described as follows:

550.0 Acute appendicitis without mention of peritonitis.
550.1 Acute appendicitis with peritonitis.
551 Appendicitis unqualified.
552 Other appendicitis.

In table II the numbers of cases and deaths in each sub-group of the disease are given, for each type of hospital, and for the two periods 1951 and 1953–54. The excess mortality is found in both periods in acute appendicitis, whether with peritonitis or not, in males and in females.

The case-fatality in appendicitis with peritonitis is much higher than in the uncomplicated disease. The

TABLE V—NUMBER OF CASES OF PERFORATED PEPTIC ULCER, NUMBER OF DEATHS, AND CASE-FATALITIES IN TEACHING AND NON-TEACHING HOSPITALS, BY AGE OF PATIENT: MALES, 1951 AND 1953–54

Age (yr.)	1951				1953–54			
	T.H.		Non-T.H.		T.H.		Non-T.H.	
	Cases (and deaths)	Case-fatality (%)	Cases (and deaths)	Case-fatality (%)	Cases (and deaths)	Case-fatality (%)	Cases (and deaths)	Case-fatality (%)
< 45	456 (15)	3·3	132 (5)	3·8	66 (1)	*1·5*	103 (1)	*1·0*
45 –	393 (30)	7·6	132 (14)	10·6	59 (5)	8·5	119 (15)	12·6
65 +	107 (25)	23·4	43 (19)	44·2	19 (6)	31·6	58 (17)	29·3
Not stated	38	..	1	..	..	..	..	..
All ages	994 (70)	7·0	308 (38)	12·3	144 (12)	8·3	280 (33)	11·8

two types of hospital agree fairly closely in the proportions of their total cases reported as having peritonitis. These are for males 14% in 1951 and 13% in 1953–54 in the teaching hospitals, and 15% in 1951 and 11% in 1953–54 in the non-teaching. Further, after childhood the proportions are similar at different ages. The figures for males in 1953–54 given in table III are an example, those for 1951 and for females being comparable. There were so few deaths among the teaching-hospital patients in the 1953–54 sample that rates based on the experience of these two years alone are of limited value. If the material from the two periods of observation is amalgamated, the case-fatality for appendicitis with peritonitis among males treated in the non-teaching hospitals in the samples is 6·8%, and when "standardised" for age this rate becomes 6·6%. The corresponding figure for the teaching hospitals was 3·3% ($0{\cdot}03>p>0{\cdot}02$).

In table IV the case-fatalities for the two types of hospital are given for males at different ages during the three years. So far as this information goes, it appears that the excess fatality in the non-teaching hospitals is not confined to any particular age-group.

TABLE VI—NUMBER OF CASES OF ACUTE APPENDICITIS WITH PERITONITIS, AND OF PERFORATED PEPTIC ULCER, NUMBER OF DEATHS, IN TEACHING AND NON-TEACHING HOSPITALS, BY DURATION OF STAY IN HOSPITAL: MALES, 1953–54

No. of complete days of stay	Acute appendicitis with peritonitis				Perforated peptic ulcer			
	No. of cases at beginning of period (and deaths during it)		Case-fatality (%) during period		No. of cases at beginning of period (and deaths during it)		Case-fatality (%) during period	
	T.H.	Non-T.H.	T.H.	Non-T.H.	T.H.	Non-T.H.	T.H.	Non-T.H.
0–3	77 (1)	190 (7)	*1·3*	3·7	144 (3)	280(18)	*2·1*	6·4
4–28	76 (1)	183 (6)	*1·3*	3·3	140 (8)	257(14)	5·7	5·4

TABLE VII—NUMBER OF CASES OF HYPERPLASIA OF PROSTATE, NUMBER OF DEATHS, AND CASE-FATALITIES IN TEACHING AND NON-TEACHING HOSPITALS, BY AGE OF PATIENT: 1951 AND 1953–54

Age (yr.)	1951				1953–54			
	T.H.		Non-T.H.		T.H.		Non-T.H.	
	Cases (and deaths)	Case-fatality (%)	Cases (and deaths)	Case-fatality (%)	Cases (and deaths)	Case-fatality (%)	Cases (and deaths)	Case-fatality (%)
< 55	92 (0)	*0*	27 (1)	*3·7*	19 (0)	*0*	31 (0)	*0*
55 –	405 (4)	*1·0*	131 (8)	6·1	66 (0)	*0*	153 (4)	*2·6*
65 –	660 (41)	6·2	280 (48)	17·1	138 (6)	4·3	296 (24)	8·1
75 +	347 (54)	15·6	169 (48)	28·4	69 (6)	8·7	255 (42)	16·5
Not stated	10	..	1	..	..	..	..	..
All ages	1514 (99)	6·5	608(105)	17·3	292 (12)	4·1	735 (70)	9·5

There were no deaths among females treated in teaching hospitals in the 1953–54 sample. In 1951 the non-teaching-hospital case-fatality for appendicitis with peritonitis was 8·2%, and when "standardised" this became 8·6%; the corresponding 1951 figure for teaching hospitals was 4·2%.

Perforated Peptic Ulcer

Separate figures are not available for gastric and duodenal ulcers. Table V sets out the numbers of male cases and deaths from perforated peptic ulcer, by age, for the two types of hospital in 1951 and 1953–54. The differences between the case-fatalities in the teaching and non-teaching hospitals are smaller than in appendicitis, and not so regular. In 1951 there was an excess fatality in all age-groups in the non-teaching hospitals. In 1953–54 there was a small excess in the teaching hospitals in patients over 65 (and in those under 45). There was an excess in the non-teaching-hospital patients aged 45–64. Because of the frequency and fatality of perforated peptic ulcer in this last age-range, the overall fatality in 1953–54 for the non-teaching hospitals was higher than for the teaching. On the whole there was some convergence of the record of the two types of hospital between 1951 and 1953–54.

As shown in table V, the age-distribution of the patients was not very different in the two types of hospital in 1951. In 1953–54 there was a disproportionate increase in the numbers of old men admitted to non-teaching hospitals with perforated ulcer. Rates summarising the 1953–54 experience therefore should be "standardised." The case-fatality at all ages of 11·8% in the non-teaching hospitals in 1953–54, when "standardised," becomes 9·8%. The teaching-hospital rate comparable with this is, of course, 8·3%. If the data for the three years (1951, 1953–54) are taken together, the case-fatalities were 7·2% in the teaching hospitals, and 9·7% (standardised for age) in the non-teaching ($0{\cdot}06>p>0{\cdot}05$).

An excess of moribund patients admitted to the non-teaching hospitals could account for the observed excess

TABLE VIII—NUMBER AND PERCENTAGE DISTRIBUTION OF CASES OF HYPERPLASIA OF PROSTATE IN MEN AGED 55 AND OVER, IN TEACHING AND NON-TEACHING HOSPITALS, BY AGE AND TYPE OF ADMISSION: 1953–54

Age (yr.)	T.H.						Non-T.H.					
	"Immediate" admissions		"Other" admissions		All admissions		"Immediate" admissions		"Other" admissions		All admissions	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
55 –	4	1·5	27	9·9	31	11·4	24	3·4	32	4·6	56	8·0
60 –	9	3·3	26	9·5	35	12·8	47	6·7	50	7·1	97	13·8
65 –	28	10·2	44	16·1	72	26·3	81	11·5	60	8·5	141	20·0
70 –	33	12·1	33	12·1	66	24·2	103	14·6	52	7·4	155	22·0
75 –	26	9·5	19	7·0	45	16·5	95	13·5	52	7·4	147	20·9
80 +	21	7·7	3	1·1	24	8·8	78	11·1	30	4·2	108	15·3
All ages	121	44·3	152	55·7	273	100·0	428	60·8	276	39·2	704	100·0

case-fatalities, though "moribundity," of course, is not the only cause of death in the first day or two in hospital. Such a mechanism may have operated in perforated ulcer (table VI) during 1953–54 (although not, as a matter of fact, in 1951).

In the three years there were 143 cases of perforated peptic ulcer in females of all ages, with 19 deaths, reported by the teaching hospitals; and 87 cases with 11 deaths reported by the non-teaching.[3]

Hyperplasia of the Prostate

The case-fatality among men admitted in 1951 and 1953–54 with a diagnosis of hyperplasia of the prostate is shown in table VII. The more favourable experience of patients admitted to teaching hospitals is found at all ages in 1951, and after 55 years in 1953–54. The 1953–54 data can be divided into narrower age-groups than those of 1951, and the admissions in these years were separated into "immediate" and "others." Detailed analysis of the 1953–54 cases (table VIII) shows that the teaching hospitals had a twofold advantage: a smaller proportion of their cases were in the older age-groups, and a larger were admitted other than "immediately." The case-fatality in the non-teaching hospitals in 1953–54, standardised for age and type of admission, was 7·6% the comparable teaching-hospital rate being 4·1% ($0{\cdot}03 > p > 0{\cdot}02$). The case-fatality at ages 65–74 years alone in the non-teaching hospitals, standardised for age and

TABLE IX—NUMBER OF CASES OF HYPERPLASIA OF THE PROSTATE ADMITTED "IMMEDIATELY," NUMBER OF DEATHS AND CASE-FATALITIES IN TEACHING AND NON-TEACHING HOSPITALS, BY DURATION OF STAY IN HOSPITAL: 1953–54

No. of complete days of stay	No. of cases at beginning of period (and deaths during it)		Case-fatality (%) during period		% of those admitted still in hospital at beginning of period	
	T.H.	Non-T.H.	T.H.	Non-T.H.	T.H.	Non-T.H.
0–3	126 (2)	444 (9)	*1·6*	2·0	100	100
4–7	120 (4)	416 (7)	*3·3*	1·7	95	94
8–14	110 (1)	387 (13)	*0·9*	3·4	87	87
15–21	92 (1)	297 (5)	*1·1*	1·7	73	67
22–28	62 (0)	231 (4)	*0*	*1·7*	49	52
29+	40 (1)	147 (10)	*2·5*	6·8	32	33
All periods	126 (9)	444 (48)	7·1	10·8	..	..

type of admission, was 7·0% compared with a teaching-hospital rate of 4·3%.

In table IX the fatalities at various periods after admission are given, and the durations of stay of the patients admitted "immediately" to the two types of hospital. There is no evidence from this, either that the non-teaching hospitals received an excessive proportion of those in extremis, or that the teaching hospitals were able to discharge rapidly many who would soon die elsewhere.

The case-fatality in both types of hospital fell between 1951 and 1953–54, the decline being sharper in the non-teaching hospitals. In the population as a whole the mortality ascribed to hyperplasia of the prostate is falling steadily (G.R.O. 1956b).

Discussion

The case-fatalities given in this paper are mostly based on small numbers of deaths, and some of the differences between the rates for teaching and non-teaching hospitals are not "significant" in the usual statistical sense. It seems unlikely, however, that such consistent differences could have been found between the two types of hospital, independent of age, sex, and what indications there are of the severity of the diseases and type of admission, if the differences were not in fact real. When the data on

3. The case-fatality in both sexes in 1951 (the only year for which we have data) from peptic ulcer without perforation was substantially higher in the non-teaching hospitals.

TABLE X—NUMBER OF CASES OF DIABETIC COMA, AND OF OTHER COMPLICATIONS OF DIABETES, NUMBER OF DEATHS, AND CASE-FATALITIES, IN TEACHING AND NON-TEACHING HOSPITALS, BY SEX: 1951 AND 1953–54

Complication	1951				1953–54			
	T.H.		Non-T.H.		T.H.		Non-T.H.	
	Cases (and deaths)	Case-fatality (%)	Cases (and deaths)	Case-fatality (%)	Cases (and deaths)	Case-fatality (%)	Cases (and deaths)	Case-fatality (%)
Males:								
Coma	99 (8)	8·1	27 (7)	25·9	11 (1)	*9·1*	30 (6)	20·0
Other	197 (9)	4·6	39 (6)	15·4	27 (1)	*3·7*	54(12)	22·2
Females:								
Coma	128 (22)	17·2	30 (7)	23·3	21 (0)	*0*	35 (5)	14·3
Other	333 (22)	6·6	68 (7)	10·3	50 (1)	*2·0*	74 (3)	*4·1*

diabetic coma given in appendix I are included, of the 17 independent comparisons of rates in the present report that are based on 5 or more deaths, the advantage lay with the teaching hospitals in 16. In view of the importance of the question, and the possible size of the differences, further and fuller inquiries clearly are necessary.

The data at present available give little or no indication of the relative importance in the production of this excess fatality of factors associated with the patients and their condition, and of factors connected with the treatment that they received. Differences in the age of the patients admitted to non-teaching hospitals do not explain the excess fatality. The proportion of cases admitted "immediately" tells little about the severity of the disease, and there is no direct information about the state of patients at admission. All the surgeons we have consulted agree in their impression that patients admitted to non-teaching hospitals for prostatectomy are on average in poorer physical condition than those who come into teaching ones; and, in general, that there may be stricter criteria of selection for this operation in the teaching hospitals. This is a point needing further inquiry to resolve, and if confirmed would have its own, and serious, implications. No-one has been able to suggest to us how such a selection of cases might be working in acute appendicitis with peritonitis.

In addition to information about the length of stay of fatal cases (tables VI and IX), another measure of the severity of the disease in patients admitted to the two types of hospital is given by the proportions suffering from appendicitis who had peritonitis. This (table III) does not suggest that the non-teaching hospitals are at a particular disadvantage in relation to appendicitis because, for instance, of delayed admission of patients. Too few facts, however, are available for any proper analysis of these aspects of the problem. Studies of the needs of the community for hospital care, and of how

TABLE XI—NUMBER OF CASES OF DIABETIC COMA, AND OF OTHER COMPLICATIONS OF DIABETES, NUMBER OF DEATHS, AND CASE-FATALITIES, IN TEACHING AND NON-TEACHING HOSPITALS, BY AGE: BOTH SEXES, 1951 AND 1953–54 DATA AMALGAMATED *

Complication	Age (yr.)	T.H.		Non-T.H.	
		Cases (and deaths)	Case-fatality (%)	Cases (and deaths)	Case-fatality (%)
Coma ..	Under 45	141 (9)	6·4	48 (6)	12·5
	Over 45	113(22)	19·5	74(19)	25·7
Other ..	Under 45	80 (1)	*1·3*	29 (0)	*0*
	Over 45	522(32)	6·1	206(28)	13·6

* The number of cases in this table does not agree with those of table X since "not stated" ages have not been included here.

these are being met, need to take account of a wide variety of such factors. The difference in staffing between different types of hospital shown in appendix II is another factor, but we have no evidence how important. We are diffident therefore about giving these figures on staffing (tables XIIa–c), especially as there are no corresponding data on the other, and it may well be more important, factors in the situation. Moreover, it is not possible to make any correction of the staffing ratios for such things as the highly specialised treatment and teaching and research responsibilities in teaching hospitals.

Some investigations of the efficiency of hospitals have been done in this country (Farr 1861, Nightingale 1871, Simon 1863), and in the United States (Kohl 1955, Lembcke 1952, Rosenfeld 1957). There is a need for clinical and epidemiological studies that are adequate to elucidate the present situation.

Summary

The case-fatality in hospital has been calculated from the statistical material provided by the hospital inpatient morbidity inquiries of the General Register Office in 1951 and 1953–54. The samples were drawn differently for these two periods, but the results are similar. In males, at all ages, in the three years 1951, 1953, 1954, together, the case-fatality from appendicitis with peritonitis was 3·3% in teaching hospitals, and 6·6% in non-teaching hospitals, the latter rate being standardised for age. For perforated peptic ulcer the case-fatality in males during these three years was 7·2% in teaching, and (standardised for age) 9·7% in non-teaching hospitals. In 1953–54 the case-fatality from hyperplasia of the prostate was 4·1% in teaching, and (standardised for age and type of admission) 7·6% in non-teaching, hospitals. Comparable differences were found in diabetic coma.

The samples used in these studies are small and not random, but it is believed that they are sufficiently representative for the observations to require further and fuller inquiries. As evidence of the representativeness of the samples, it may be mentioned that the hospitals in 1953–54 were similar in size to those of the whole country; the number of house-officers and nurses per 100 beds was almost identical with the national average for 1953; and calculation of "expected" numbers of deaths for England and Wales on the basis of the experience in this 1953–54 sample gave figures very close to (or better than) the actual figures of hospital deaths recorded by the Registrar-General.

A situation in 1951 and 1953–54 has been described, but because of the paucity of data very little can be attempted by way of explanation. Nothing is known of the situation as it is today.

We are much obliged to the General Register Office and to the Ministry of Health for information. Mr. J. D. Fergusson and Dr. H. Joules of the Central Middlesex Hospital, and Dr. D. A. Jennings and Mr. J. E. Richardson of The London Hospital, made very useful criticisms of earlier versions of the paper. We are grateful also to many surgeons and other hospital staff in various parts of the country who so freely discussed these problems with us. Our colleagues in the Social Medicine Research Unit gave us much help.

TABLE XIIa—NUMBER OF SURGEONS PER 1000 SURGICAL BEDS, IN TEACHING AND NON-TEACHING HOSPITALS: ENGLAND AND WALES, 1953

Staff	T.H.	Non-T.H.
Consultants	22	16
Senior hospital medical officers	0·4	2
Senior registrars	18	3
Registrars, &c.	25	16
House-officers (per 1000 beds of all types)	38	14

This tabulation includes all surgeons, specialist and general, and all surgical beds.

Part-time consultants and S.H.M.O.s have been "converted" to full-time equivalent on the arbitrary basis of 40 hours per week.

Part-time registrars have been "converted" to full-time on the basis of a 50-hour week.

The figures for house-officers are the numbers of *all* house-officers in general teaching and non-teaching hospitals per 1000 beds of *all* types in these hospitals, and not merely surgical beds.

The number of house-officers per 1000 beds in the general hospitals included in the 1953–54 samples on which this study is based is almost identical with that in the hospitals of the country as a whole.

TABLE XIIb—NUMBER OF ANÆSTHETISTS PER 1000 SURGICAL BEDS IN TEACHING AND NON-TEACHING HOSPITALS: ENGLAND AND WALES, 1953

Staff	T.H.	Non-T.H.
Consultants	15	8
Senior hospital medical officers	1	3
Senior registrars	4	0·3
Registrars, &c.	14	6

This tabulation includes all anæsthetists, and all surgical beds.

Conversions to full-time have been made on the same basis as in table XIIa.

TABLE XIIc—NUMBER OF NURSES PER 100 BEDS IN TEACHING AND NON-TEACHING GENERAL HOSPITALS: ENGLAND AND WALES, 1953

T.H.		Non-T.H.	
Full-time	Part-time	Full-time	Part-time
82	3	51	6

No data are available on the distribution by surgical or medical beds, or on the whole-time equivalent of the "part-timers."

The number of full- and part-time nurses per 100 beds in the hospitals included in the 1953–54 samples on which this study is based is almost identical with that in the hospitals of the country as a whole.

Appendix 1:

CASE-FATALITY—GENERAL PICTURE IN 1951

The published material for 1951 was divided into 54 major diseases or disease-groups. In 46 of the 54 the case-fatality was higher in both sexes in the non-teaching hospitals; in 8 the case-fatality was higher in the teaching hospitals in one sex or both.

The eight conditions can be divided into two groups: (*a*) five where the numbers are so small that the differences cannot be evaluated; and (*b*) others. In the first group are "infectious disease commonly arising in the intestinal tract" with 1 death among 116 females treated in the teaching hospitals, and 0 among 183 treated in the non-teaching. Similarly there were 0 deaths among 229 females with eye diseases treated in non-teaching hospitals, compared with 6 among 5775 treated in teaching hospitals. There was 1 death among 279 males treated in teaching hospitals for non-malignant disease of the tongue and buccal cavity, compared with 0 among 39 treated in non-teaching hospitals. There was 1 death among 914 females treated in teaching hospitals for non-malignant disease of the breast, compared with 0 among 176 treated in non-teaching hospitals. Mental hospitals were excluded from this study, and there were only 39 male cases of mental disease or mental deficiency reported by the non-teaching hospitals, with 0 deaths. In the teaching hospitals there were 425 cases with 4 deaths.

Group (*b*) may be summarised as follows: there was a higher death-rate in the teaching hospitals from pemphigus, erythema multiforme, lupus erythematosus, scleroderma, and dermatomyositis. In 1951, the year to which these data refer, cortisone was available only at a small number of hospitals, mainly teaching. There was also a higher death rate in the teaching hospitals from myasthenia gravis; although there were few non-teaching hospital cases, this also seems likely to be the result of selection. In the group "all other infectious and parasitic diseases" there was an excess death rate in both sexes in the teaching hospitals. There were 13 deaths in teaching hospitals out of 134 cases of meningococcal infection, compared with 6 out of 80 in the non-teaching hospitals; and 4 out of 108 cases of acute infectious encephalitis in teaching hospitals compared with 1 out of 98 in non-teaching hospitals. There were also 18 deaths out of 481 cases of the sub-group of the "remaining infectious and parasitic diseases" in the teaching hospitals, compared with 5 out of 279 in the non-teaching. No further details are given about these conditions.

In some conditions, such as cerebral hæmorrhage and respiratory tuberculosis, there was an excess fatality in the non-teaching hospitals to which selection of cases must surely make a large contribution. There were several conditions where selection seemed less likely to be important, but for which there is too little information. Thus in 1951 the case-fatality for head injuries was higher in the non-teaching hospitals (Morris 1957), and this was found again in 1953–54. No information is available, however, about the type of head injury admitted to the different hospitals. There was an excess case-fatality in coronary thrombosis treated in non-teaching hospitals in 1951, which was not repeated in 1953–54. This excess fatality in 1951 was found at periods of 0–3 days, 4–7 days, 8–28 days, and 29 days and over. Many conditions such as burns, intussusception, strangulated hernia, uterine fibroids, thyrotoxicosis, other thyroid disease, and pernicious anæmia had an excess case-fatality in the non-teaching hospitals in 1951, but the number of deaths is small and they were therefore not investigated in 1953–54.

Diabetes

The case-fatality from diabetic coma was higher in both sexes, and in both periods, in the non-teaching hospitals (table X); and the difference was larger in the younger patients (table XI). The case-fatality from the other complications of diabetes was also higher in the non-teaching hospitals. Numbers are too small for more detailed analysis.

Appendix II:

STAFF

The figures (tables XIIa–c) on the staffing of teaching and non-teaching hospitals have been extracted from the latest publication on the subject (Ministry of Health 1956b). These figures refer of course to the whole country and not merely to the hospitals included in the present study.

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NOT BY BEDS ALONE

The Minister's Advice on the Care of the Elderly

ONE of our most important responsibilities towards old people is to provide hospital beds for them; perhaps an even more important responsibility is to see that they use these beds as seldom and as late in their lives as possible. To achieve this, the hospitals and the local authorities must work together to help old people to stay in their own homes as long as they are fit, and no longer. In two circulars issued last week, one to hospital authorities [1] and one to local authorities,[2] the Minister of Health accepted the need to develop the services for old people as one of the most urgent tasks of the National Health Service. But this did not in his view mean the provision of more hospital beds for the chronic sick, but more discriminating use of the beds that we have, supplemented by better domiciliary and welfare services.

He asked the different authorities to join together to provide a single comprehensive service for old people. Within the present administrative framework effective cooperation was possible. One stumbling-block to a truly comprehensive service was what he described as "the lack of a clear perception by hospital and welfare authorities of their respective responsibilities." The main divisions were clear; as guidance for more difficult borderline cases he offered the following definitions:

Apart from the active elderly person who is in need of residential care and who is clearly the responsibility of the welfare authority, the latter's responsibility also extends to the following:

(i) Care of the otherwise active resident in a welfare home during minor illnesses which may involve a short period in bed.

(ii) Care of the infirm (including the senile) who may need help in dressing, toilet, etc., may need to live on the ground floor because they cannot manage stairs, and may spend part of the day in bed (or longer periods in bad weather).

(iii) Care of those elderly persons in a welfare home who have to take to bed and are not expected to live more than a few weeks (or exceptionally months) and who would, if in their own homes, stay there because they cannot benefit from treatment or nursing care beyond what can be given at home, and whose removal to hospital away from their familiar surroundings and attendants would be felt to be inhumane.

All these are persons for whom any necessary nursing care would be given by relatives, etc., with the help or advice of the home nurse if they were living in their own homes. In welfare homes that care should be given by attendants, assisted or advised by the visiting home nurse in the small welfare home, or by a small staff with nursing qualifications or experience in the larger homes.

It is not regarded as the responsibility of the welfare authority to give prolonged nursing care to the bedfast (except in those in (iii) above), nor is it desirable that separate "infirmary wards," in which patients from other homes are concentrated, should be created in large homes.

Apart from the acute sick and others needing active treatment, who are clearly the responsibility of the hospital authority, the latter's responsibility also extends to the following:

(i) Care of the chronic bedfast who may need little or no medical treatment but do require prolonged nursing care over months or years.

(ii) Convalescent care of the elderly sick who have completed active treatment but are not yet ready for discharge to their own homes or to welfare homes.

(iii) Care of the senile confused or disturbed patient who is, owing to his mental condition, unfit to live a normal community life in a welfare home.

It is not regarded as the responsibility of the hospital authority to give all medical or nursing care needed by an old person, however minor the illness or however short the stay in bed; nor to admit all those who need nursing care because they are entering upon the last stage of their lives.

One of the best ways of achieving cooperation was the joint appointment of a hospital geriatric physician by regional boards and by local authorities. The Minister was insistent that every hospital centre should give priority to setting up a geriatric department under the charge of a specialist.

The Minister's other recommendations to the hospitals included the development of outpatient services for the elderly. On the whole he inclined to the view that it was best for old people to have full access to the ordinary clinics rather than to attend special clinics of their own. Day hospitals could usefully supplement these clinics, especially for patients who were mentally enfeebled. Arrangements which allowed old people who were being nursed at home to be admitted to hospital for short stays gave relatives a welcome break. Medical care should also be supported by such ancillary services as chiropody, physiotherapy, and occupational therapy. Domiciliary visits eased admissions and kept the waiting-list under informed supervision. Short-stay psychiatric units were a useful addition to a geriatric department.

1. H.M.(57)86.
2. Circular 14/57.

Most of the chronic sick are elderly, but unfortunately there is a small minority of young people among them. It is, as the Minister says, "wholly unsatisfactory" for them to be nursed for, "perhaps, the greater part of a life-time in the company of older patients in all stages of terminal illness or of much greater ages." He asked regional hospital boards to consider how far these patients could be grouped together without losing touch with their own families.

The Minister reminded the local authorities that there were still many people—it had been estimated at 4500—who were occupying hospital beds but who could be in residential homes if they were available. A smaller number of people living in homes would probably benefit by being moved to hospital. These ill-used beds showed the need for closer coöperation between hospitals and the local services, which should cover not only the patients on the hospitals' waiting-lists but also the patients who had returned to their homes. Both of these groups stood in special need of the help of the domiciliary health services. These, the Minister thought, though generally adequate, were too thinly spread in some areas and he urged their continued expansion.

The advice which the Minister has offered the hospital and the local authorities was based on Dr. C. A. Boucher's report [3] on the survey of services for the chronic sick and elderly. This survey was carried out during 1955 in each hospital region by teams headed by a principal regional officer of the Ministry. The teams collected opinions as well as facts, and not the least interesting part of the report is the chapter on the views on geriatrics as a specialty. At one extreme it was held that an elderly patient should be treated in the general wards of the hospital, and geriatricians were regarded as "medical practitioners of a clinical calibre who could not always claim equality with other consultants." There was considerable prejudice against geriatric appointments and some ignorance of the possibility of reablement. On the other hand those who supported these appointments were sure that, thanks to them, the pressure on beds was relieved, and the turnover improved. Many geriatric units had been remarkably successful; some less so, perhaps because the geriatrician's responsibilities were limited to the daily treatment of patients and because there was lack of junior medical staff and an insufficiency of almoning, physiotherapy, and occupational-therapy help. Though geriatrics offers clinical opportunities of unlimited interest and wide opportunities of research, the survey found that the recruitment of junior staff remained difficult and senior staff with suitable experience were not always forthcoming. New units would entail the appointment of more physicians with a clear understanding of the social and medical problems of the elderly patient, yet the number of registrar appointments in existing units did not seem to meet the demand for senior appointments.

3. *Rep. publ. Hlth med. Subj., Lond.* no. 98, 1957. H.M. Stationery Office. Pp. 60. 3*s*.

Public Health

INFLUENZA OUTBREAK IN SINGAPORE

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AN outbreak of influenza, which seems to have begun in North China, reached Singapore in May, 1957. Influenza is not notifiable in the island and no reliable figures for overall incidence could be obtained. Moreover, a large proportion of the population does not seek Western-type medical care. Mainly for these reasons, our detailed study of the outbreak has been confined to the civilian population in the Singapore Naval Base, consisting of Naval Base workers and their dependants. The main advantages of this include fairly complete ascertainment of cases from the working population at least, reasonably reliable definition of the population at risk, and a medical service accessible to all cases.

For all cases seeking medical attention in the Naval Base, data were recorded on date of onset, age, sex, ethnic group, place of work within the Base, and whether admitted to hospital or treated at home. Pressure of clinical work made it impracticable to record further data on patients not admitted to hospital. For those admitted a record-card was designed for recording, besides the above data, details of symptoms, complications, duration and level of pyrexia, and duration of stay. In addition blood was taken from a number of the hospital patients in the acute and convalescent stages for serological examination. We present an analysis of these data, with certain other observations made in the Singapore Civilian General Hospital in the city.

Clinical Findings

For present purposes, the clinical observations relate to 298 patients with influenza admitted to the Asian hospital in the Base. Criteria of admission were difficult to specify since they depended on many factors (age of the patient, general state of health, availability of beds, &c.). Doctors were asked to assess their cases clinically in three categories—mild, moderate, and severe—but it became evident that such classification was difficult and unreliable and it was accordingly dropped.

Table I shows the distribution of the 298 admitted cases by age and sex. At the younger ages little difference is seen between the numbers of males and females, but as age increases female cases are fewer. This is probably due to a difference in the numbers seeking treatment rather than in the numbers affected. Table I also shows the duration of hospital stay by age. It is clear that hospital stay was longest in the very young and the old. Young adults had the shortest stay.

Pyrexia

All patients had pyrexia, and they were not discharged until their temperatures had returned to normal. The mean duration of pyrexia over all ages was $2{\cdot}4 \pm 0{\cdot}87$ days and it varied little with age.

The mean temperature on admission was 102·9°F and the mean highest record was 103·1°F. In 41 of the 298 cases the highest record was higher than the record on admission. Of the patients with temperatures below 100°F on admission, the temperature rose in 69% during their hospital stay,

TABLE I—HOSPITAL PATIENTS. AGE AND SEX DISTRIBUTION, AND MEAN DURATION OF HOSPITAL STAY AND OF PYREXIA

Age (yr.)	0–4	5–9	10–14	15–19	20–29	30–39	40–49	50–59	60 and over	All ages
No. of patients ..	32	49	19	27	75	64	18	11	3	298
No. of males ..	17	34	8	20	70	59	16	11	3	238
No. of females ..	15	15	11	7	5	5	2	0	0	60
Mean duration of hospital stays (days)	6·9	6·1	5·9	4·9	4·1	4·4	4·9	9·5		5·3 ± 0·24
Mean duration of pyrexia (days) ..	2·2	1·8	2·6	2·1	2·5	2·5	2·5	4·1		2·4 ± 0·87

TABLE II—COMPLICATIONS IN ASIAN HOSPITAL ADMISSIONS

Age-group	No.	Complication	Ethnic group	Sex
0–4	1	Tonsillitis	Chinese	M
	1	Conjunctivitis	Indian	,,
	1	Bronchitis	,,	,,
	2	Pneumonias	,,	,,
	1	Tracheitis	,,	F
	1	Cervical adenitis	,,	,,
5–9	1	Bronchitis and pneumonia	Indian	M
	1	Conjunctivitis	,,	,,
	1	Tonsillitis	,,	,,
	1	Bronchitis	,,	,,
	1	Pneumonia	,,	,,
	1	Pneumonia	Malay	,,
	1	Bronchitis	Indian	F
10–14	1	Pneumonia	Chinese	M
	1	Pneumonia	Indian	F
15–19	1	Bronchitis	Indian	M
	1	Bronchitis and pneumonia	,,	,,
20–29	3	Bronchitis	Indian	M
	1	Pneumonia	,,	,,
	1	Relapse influenza	,,	,,
30–39	5	Bronchitis	Indian	M
	1	Bronchitis	Malay	,,
	1	Pneumonia	Indian	,,
40–49	1	Bronchitis	Chinese	M
	1	Bronchitis	Indian	,,
	1	Pneumonia	,,	,,
50–59	3	Pneumonias	Indian	M
	2	Bronchitis	,,	,,
60 +	1	Pneumonia	Indian	M

suggesting that people admitted with low temperatures were probably in an earlier stage of their illness than those admitted with higher temperatures. Since their total number was small, it seems probable that the temperature rose rapidly with onset of the disease and remained elevated for between two and three days.

Other Symptoms

Most patients presented more than one symptom, but no particular combinations of symptoms were commoner than would be expected from their individual incidence. Apart from pyrexia, which was universal, headache was the commonest symptom (193 patients). The next commonest was sore throat (135). This symptom is not usually regarded as an important one in influenza. Cough was complained of by 93 patients and muscular pains by 55. In patients with sore throat, the pharynx usually displayed generalised inflammation.

Complications

Complications were recorded in 39 out of the 298 admitted cases (table II). As might be expected, they were commoner in the young and in the old than in young adults. In children under 5 the complication-rate was about 22%; in adults over 50 it was 43%; but in patients between the ages of 15 and 30 it was only 7%. The most important complications were pneumonia (15 cases) and bronchitis (17 cases). Complicated cases represented 13% of all admissions, and accounted for 26% of the total bed-stay attributable to the outbreak.

Among the Naval Base cases there were no deaths; indeed few deaths were reported as due to influenza at any time during the outbreak. However, although final figures are not available, it appears that the general death-rate in Singapore was higher during the month of May than is usual at that time of year. Influenza may well have accelerated death in patients with more chronic diseases.

The general impression was that, though patients were severely incapacitated by their illness, uncomplicated recovery within five days was usual.

Epidemiology

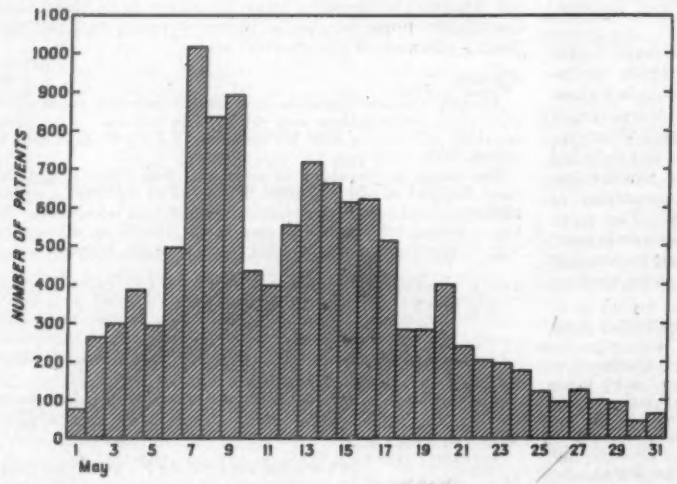
Although sporadic cases were seen in the last few days of April, the major outbreak did not start until May 1.

At the outpatient clinic of the General Hospital the greatest daily number of cases was on May 7 (see figure) but a smaller peak followed on May 13. In the Naval Base there were two peaks—on May 9 and on May 13. The significance of these later peaks is not clear; but their occurrence on a Monday, after a fall in attendances on the Saturday and Sunday, suggests that they need not be attributed to a secondary rise in attack-rate. The observation of a further slight rise in attendances at both the General Hospital and the Naval Base on Monday, May 20, reinforces this caution.

At the Naval Base cases were conveniently divisible into those among workers and those among dependants. The outbreak in dependants was later than that in workers. The interval between the median case in workers and that in dependants was three days. Cases from General Hospital attendances are not exactly divisible in this way; but they may be divided into those in adult males and those in women and children. The interval between median cases in these two groups was two days. In both the Naval Base and the General Hospital data the "dependant" groups show a shift in distribution towards the later periods when compared with the "worker" groups (table III). The shift is statistically highly significant for both sets of data. In view of the usually accepted incubation-period for influenza of twenty-four to forty-eight hours, the above data are consistent with the view that in this outbreak primary spread was largely at place of work, and that families of workers were infected secondarily mainly by introduction of infection into the family by the worker.

It is thus of interest to inquire whether differences in the intimacy of contact between members of work units and between members of a family are reflected in the attack-rates for workers and those for dependants.

In the Naval Base, overall attack-rates in work departments and among dependants were about 28% for workers and 10% for dependants. But these rates cannot be accepted unreservedly. Whereas workers who wish to be absent from work for reasons of sickness are required to attend at the surgery, dependants are under no such obligation. Of the 890 cases among dependants, 833 were among Asian dependants. Explanation of the differences in attack-rates between workers and dependants must take into account differences in status between adult males and women and children which influence attendance at surgery. Many Asian women are



Daily distribution of new cases at Singapore General Hospital, outpatients department (month of May).

TABLE III—DISTRIBUTION OF CASES DURING MAY

Naval Base						General Hospital					
Date		1–10	11–20	21–31	Whole month	Date		1–10	11–20	21–31	Whole month
Workers	No.	873	1263	324	2460	Males (aged 15 and over)	No.	1636	1382	376	3394
	%	35·49	51·34	13·17	100·00		%	48·20	40·72	11·08	100·00
Dependants	No.	162	505	191	858	Females (plus males aged 0–14 yr.)	No.	3340	3674	1061	8075
	%	18·88	58·86	22·26	100·00		%	41·36	45·50	13·14	100·00
Total	No.	1035	1768	515	3318	Total	No.	4976	5056	1437	11,469
	%	31·19	53·29	15·52	100·00		%	43·39	44·08	12·53	100·00
χ^2 for 2 degrees of freedom = 96·31 $P < 0·001$						χ^2 for 2 degrees of freedom = 46·24 $P < 0·001$					

unwilling to seek medical attention from male doctors, particularly when these doctors are Europeans. In Europeans the attack-rates in workers and dependants were about 6% and 7% respectively.

No evidence is provided that differences in intimacy of contact are reflected in differences in attack-rates.

Departments were divided according to whether workers in them worked predominantly in or out of doors, or partly indoors and partly outdoors (table IV). In general this latter category includes those who work either in workshops (indoors) or in ships (outdoors). It might be expected that indoor workers would show the highest attack-rates, but actually they had the lowest. Indoors people usually work in closer proximity and with longer contact than outdoors; and one can scarcely suppose that working indoors enhances resistance to influenza. A possible explanation for the lower incidence among indoor workers is that they are mainly clerical and in general are socio-economically more favoured than the outdoor workers, many of whom are poorly paid labourers. It was an undocumented impression in the city generally that few cases were reported from the residential areas where the better-off inhabitants live.

The attack-rate was about 29% for Asian workers and 6% for Europeans. But before this difference can be accepted as corroborating the influence of social circumstances, one must examine the possibility that it was due to differences in previous experience of influenza and consequently in immunity. Such a hypothesis is not immediately attractive, since the virus responsible for the Singapore outbreak was soon shown to be a new strain, and cross-immunity between influenza strains is usually small. The point is dealt with later in the section on serology.

Asian workers are not of course ethnically homogeneous.

In Singapore the largest group are the Chinese, who comprise some 80% of the population. Other Asian groups are Indians (who include people who originate from the subcontinent of India and from Ceylon), and Malaysians (who include people originating from Malaya, Indonesia, and British North Borneo). Other ethnic groups are not large in number. But in the Naval Base the proportions differ from those in the city. The largest group among Naval Base civilians are Indians (4519), followed by Chinese (2465), Malaysians (1543), and Eurasians (24). There are 469 European workers, who are mainly in relatively senior executive and administrative posts.

Attack-rates varied between the various groups. Chinese had a lower attack-rate (21%) than Indians (32%) or Malaysians (31%). Since there is strong association between ethnic group and choice of occupation, we must inquire whether differences in attack-rates between departments can be attributed to differences in their ethnic-group composition.

Table IV shows that the difference in attack-rates between indoor and outdoor workers is largely eliminated in the Chinese group but is still obvious for Indians and Malaysians. The number of Eurasians is too small for the differences to be important.

The data can be used to calculate weighted attack-rates for the work-unit divisions, eliminating the contribution of differences in ethnic-group distribution to the differences in attack-rate. Weighted attack-rates were about 21% for indoor workers, 32% for intermediate workers, and 27% for outdoor workers. The low rate for indoor workers is maintained, and therefore cannot be attributable to a predominance of ethnic groups with a low attack-rate.

These results suggest that different ethnic groups experience different attack-rates, and that workers from different socio-economic classes have different attack-rates.

Part of the ethnic group differences may be attributable to differences in the extent to which different ethnic groups seek Western medical attention. Traditional medicine flourishes more among the Chinese than in other groups. But it is difficult to believe that this accounts for much of the difference, since absence from work without attendance at surgery involves loss of earnings.

A question of some importance is the age-distribution of attack-rates.

Unfortunately it was not possible to obtain a distribution by year of age, either of the cases or of the population at risk.

TABLE IV—ATTACK-RATES IN ETHNIC GROUPS BY PLACE OF WORK

Place of work	Asians											Europeans			Total		
	Chinese		Indians		Malaysians		Eurasians		Total								
	No. at risk	Attack rate (%)	No. at risk	Attack rate (%)	No. at risk	Attack rate (%)	No. at risk	Attack rate (%)	No. at risk	No. of cases	Attack rate (%)	No. at risk	No. of cases	Attack rate (%)	No. at risk	No. of cases	Attack rate (%)
Indoors ..	239	18·8	949	24·7	319	15·7	6	16·7	1513	330	21·8	133	5	3·8	1646	335	20·4
Intermediate	2045	22·1	2650	35·5	690	34·8	15	20·0	5400	1034	30·3	292	23	7·9	5692	1657	29·1
Outdoors ..	181	12·7	920	30·9	534	35·6	3	66·7	1638	499	30·5	44	2	4·5	1682	501	29·8
Total ..	2465	21·1	4519	32·3	1548	31·1	24	25·0	8551	2463	28·8	469	30	6·4	9020	2493	27·6

TABLE V—DISTRIBUTION OF ASIANS BY AGE AND PLACE OF WORK

Place of work	—	Age				Total
		0–19	20–29	30–39	40+	
Indoors	No.	43	356	618	496	1513
	%	2·8	23·5	40·8	32·8	100
Intermediate	No.	249	1608	1598	1945	5400
	%	4·6	29·8	29·6	36·0	100
Outdoors	No.	32	396	694	516	1638
	%	1·9	24·2	42·4	31·5	100
Total	No.	324	2360	2910	2957	8551
	%	3·8	27·6	34·0	34·6	100

When cases were recorded, we expected to be able to ascertain the age-distribution of the population at risk: accordingly, cases were recorded as falling in the age-groups 0–20, 21–30, 31–40, and 41 and over. It later proved possible to obtain the age-distribution of the population only by the groups 0–19, 20–39, 30–39, and 40 and over. Hence age-specific attack-rates cannot be calculated precisely. If the groupings are used to derive approximate attack-rates by age, this will tend to exaggerate the rates in the young and underestimate them in the old. The middle ranges will probably be affected only slightly. However, with these reservations in mind, the approximate attack-rates show a striking pattern.

For patients under 20 the rate was 89%; for those aged 20–30 it was 48%; for those aged 30–40 it was 22%; and for the oldest age-group it was 11%. So striking a trend is unlikely to be more than to a slight extent due to the effect of incomparability of the groupings available. It seems certain that the attack-rates declined consistently with age.

This finding raises the question of how far the differences in attack-rate between indoor and outdoor workers, and between different ethnic groups, is attributable to differences in the age-distribution of different workers in different places of work, and of different ethnic groups.

The non-comparability of the groupings for cases and for the population at risk does not permit the calculation of age-standardised attack-rates. But the age-distribution of the population at risk does not vary much between the different places of work. The small differences in age-distribution are in fact in a direction which would suggest that the differences in attack-rates between indoor and outdoor workers have been reduced by not taking into account the age-distributions of workers in the three groups (table v).

Similar examination of the distributions by age and ethnic groups (table VI) suggests that the low attack-rate among Chinese, as compared with other Asian groups, cannot be attributed to differences in age-distribution. In fact, when Chinese and Indians are compared it is evident that if the rates were standardisable for age the difference would be accentuated. But Asians as a group are considerably younger than the Europeans. Small numbers in the younger age-groups among Europeans, and the non-comparability of age-grouping of cases and population, make it undesirable to attempt to eliminate age-distribution differences by standardisation; but comparison of approximate attack-rates between Asians and Europeans for the older age-groups (table VII) shows that the difference is considerable, and that Asians in these age-groups experience much higher attack-rates. It is unlikely therefore that the overall difference in attack-rates between Asians and Europeans is largely attributable to the difference in age-distribution.

TABLE VI—DISTRIBUTION OF WORKING POPULATION BY AGE AND ETHNIC GROUP

—	—	Age				Total
		0–19	20–29	30–39	40+	
Chinese	No.	154	710	658	943	2465
	%	6·2	28·8	26·7	38·3	100
Indian	No.	104	1120	1591	1704	4519
	%	2·3	24·8	35·2	37·7	100
Malaysian	No.	63	525	657	298	1543
	%	4·1	34·0	42·6	19·3	100
Eurasian	No.	3	5	4	12	24
	%	12·5	20·8	16·7	50.0	100
European	No.	7	48	204	210	469
	%	1·5	10·2	43·5	44·8	100
Total	No.	331	2408	3114	3167	9020
	%	3·7	26·7	34·5	35·1	100

The decline in attack-rates with age suggests differences between different age-groups either in exposure risk or in immunity. Similar trends in attack-rates are usually explicable in terms of the acquisition by the older groups of some specific immunity.

Serological Findings

In view of the finding that attack-rates vary with ethnic group (particularly between Asians and Europeans) and to some extent with socio-economic circumstances, the question arises whether the variation is attributable to differences in immunity status. This question is of even greater interest because the virus responsible for the Singapore outbreak was of a previously unknown strain.

Investigation

Sera.—Paired sera were obtained from 46 male Asian patients, clinically diagnosed as having influenza. After the outbreak was over, single specimens were obtained from 47 Asian patients not clinically diagnosed as having influenza. In addition, 56 sera were obtained from European volunteers. All sera were stored at −20°C until used.

TABLE VII—ATTACK-RATES IN OLDER AGE-GROUP BY ETHNIC GROUP

—	Patients aged 31 and over (a)	Population at risk aged 30 and over (b)	Approximate attack-rate $\left(\frac{a}{b}\times 100\right)$
Asians	1017	5867	17·3%
Europeans ..	20	414	4·8%

Treatment.—Non-specific inhibitors were removed from sera by treatment of 0·5 ml. of serum with 1·0 ml. of 0·015 M potassium metaperiodate (KIO_4). After overnight cold storage of the serum, 1 ml. of glycerol was added. The concentration of iodate required was determined by trial on normal rabbit serum.

Virus.—The strain used was isolated during the present outbreak elsewhere in Singapore. This strain, similar to that recovered from a case in the Naval Base, has been designated A/Singapore/1/1957 by the World Influenza Centre. In this paper we shall call it Singapore virus.

FM-1, PR8, WS, and LEE strains were kindly provided by Dr. Alick Isaacs of the World Influenza Centre.

Allantoic fluids of eggs infected with these viruses were stored at −20°C until used. Hæmagglutinin titres have been maintained for over a month.

Cells.—Fowl red cells were stored in Alsever's solution. Before use cells were washed three times in saline and then made up in 0·1% suspension. A densitometer was used for standardisation.

Hæmagglutination inhibition tests.—The pattern test was used. To 0·25 ml. of diluted serum was added 0·25 ml. of virus, containing five agglutinating doses. To this was added 0·25 ml. of fowl-cell suspension. A serum was regarded as positive if there was more than 50% of inhibition at a dilution of 1/10.

With each batch of sera tested, controls of normal rabbit sera were included to verify that all non-specific inhibitors had been removed by the iodate treatment. Known positive sera included showed that titres were reproducible within a factor of two.

TABLE VIII—RESULTS OF H.A.I. TESTS ON ASIAN AND EUROPEAN SERA

—	Age-group	No. tested	Virus inhibited (nos. of positive sera)				
			Singapore	FM-1	PR 8	WS	LEE
VIIIa. Asians admitted to hospital on account of influenza	15–19	6	5	5	3	4	1
	20–24	7	7	7	7	4	3
	25–29	13	7	13	10	9	6
	30–34	6	3	6	5	4	5
	35–39	8	6	6	6	8	6
	40 —	6	3	5	4	5	4
	Total	46	31	42	35	34	25
VIIIb. Asians asymptomatic during outbreak	20–24	4	1	4	3	1	2
	25–29	5	2	3	3	3	2
	30–34	3	0	3	3	3	3
	35–39	10	0	8	10	9	8
	40–44	8	2	7	8	5	3
	45–49	11	1	5	9	7	7
	50 —	6	0	4	5	3	1
	Total	47	6	34	41	31	26
VIIIc. Europeans	15–19	10	0	6	9	2	3
	20–24	22	1	15	14	6	7
	25–29	10	3	7	6	7	5
	30–34	4	1	2	4	3	2
	35–39	6	3	3	2	5	5
	40 —	4	0	2	2	1	1
	Total	56	8	35	37	24	23

Results

In the first group all but two of the acute sera did not inhibit the Singapore strain (table VIII); therefore the positives recorded in table VIIIa under "Singapore" were found almost exclusively in the convalescent sera. On the other hand, all but two pairs of sera showed no significant rise for any of the other viruses, and the positives recorded in the other columns in VIIIa indicate titres in acute and convalescent sera differing by less than fourfold. One pair of sera showed significant rise (1/10 to 1/60) for WS strain, and another (1/10 to 1/80) for LEE strain. It is not known whether these rises were due to experimental errors or indicated infection by these viruses during the outbreak.

The surprising discovery was the widespread distribution of inhibitors to viruses other than the Singapore virus. At the beginning of the work it was not known that Singapore virus was of a radically new A antigenic type; but, even when this was known, it was thought possible that lower attack-rates reported in Europeans might be due to some cross-immunity from other influenza viruses with which they had had contact in Europe.

There had been no notable outbreak of influenza in Singapore since the end of the war, and the widespread distribution of inhibitors to FM-1, as well as to PR8, WS, and LEE, indicates that influenza viruses had been circulating quite freely in Singapore without producing a recognisable outbreak. The lower attack-rate in the Europeans was not due to any acquired immunity detectable by hæmagglutination inhibition tests.

Asians, whether clinically attacked in the present outbreak or not, had a significantly higher proportion of positive reactions to FM-1, PR8, WS, and LEE viruses than Europeans (table IX). Asian and European sera tested may be regarded as fair samples of the population; for the method of sampling is independent of their history of previous contact with these viruses.

TABLE IX—COMPARISON OF RESULTS AGAINST 4 VIRUSES

—	FM-1			PR8			WS			LEE		
	−	+	% positive	−	+	% positive	−	+	% positive	−	+	% positive
Asians (93) ..	17	76	81·7	17	76	81·7	28	65	70	42	51	54·8
Europeans (56)	21	35	62·5	19	37	66·1	32	24	42·9	33	23	41·1
χ^2 for 1 degree of freedom ..	6·79			4·67			10·61			2·65		
P	0·01			0·05			0·01			0·2–0·1		

We may regard a person whose serum inhibits several viruses as having had more contact with influenza viruses in the past than a person whose serum inhibits fewer viruses. The European sera reacted with relatively fewer viruses than the Asian sera (table X). The inference is that the Asian population has had in the past more contact with FM-1, PR8, WS, and LEE viruses.

This difference is more striking when the results of tests on 93 Asian sera are classified according to whether or not they inhibited the Singapore virus (table X). Analysis of the distribution of sera inhibiting none, one, two, or three viruses, other than Singapore virus, showed no significant difference between the two groups.

Discussion

The results indicate that previous experience of influenza virus conferred no protection against an attack by the Singapore virus. The lack of cross-protection conforms with the general behaviour of antigenic variants of influenza viruses.

The low attack-rate reported in Europeans cannot be explained on immunological grounds, but the data yield a further inference. The higher attack-rate in the Asian population is associated with a higher rate of inhibitors in the serum samples. This suggests that the persons attacked are from a population which has been exposed freely to influenza viruses in the past. Factors which promoted free contact with influenza viruses in the past may have operated the same way in the recent outbreak and resulted in a higher attack-rate in the Asian than in the European population. Although, in the Naval Base, Asians and Europeans work side by side, allowing ample contact and opportunities for infection to spread, such contact was apparently insufficient to infect many Europeans.

TABLE X—COMPARISON OF SERA INHIBITING NONE, 1, 2, 3, OR ALL OF FM-1, PR8, WS, AND LEE VIRUSES

No. of viruses inhibited		0	1	2	3	4	Significance
56 European sera ..		8	11	13	14	10	χ^2 for 4 degrees of freedom = 12·05
93 Asian sera ..		2	8	18	36	29	0·02 > P > 0·01
93 Asian sera	37 inhibiting Singapore virus	0	4	6	16	11	χ^2 for 4 degrees of freedom = 0·5
	56 not inhibiting Singapore virus	2	4	12	20	18	P > 0·9

Another interesting fact is that though there has been no outbreak of influenza in Singapore in the past twelve years, the Asian population has been exposed to influenza viruses so often that, for example, 76 out of 93 sera inhibited FM-1 virus. In the adjoining Federation of Malaya, both A-prime strains and B strains have been isolated from sporadic outbreaks in recent years.[1] The virulence and communicability of influenza viruses have been so low that their presence did not affect the normal life of the community. The Singapore strain, however, is so exceptionally infectious that it spreads in an epidemic fashion.

Whereas it seems that communicability of the virus involved in this outbreak is high, wide differences in attack-rate were found in different groups. Since it seems that these differences are not attributable to differences in previously acquired immunity, we are left with the hypothesis that susceptibility to infection differs between different groups and has a basis other than acquired serological immunity. Ethnic-group differences are complex in that they include genetic, social, cultural,

1. Gordon Smith, C. E., Turner, L. H., Helliwell, C. J. V. *Brit. med. J.* 1957, i, 1412.

occupational, and dietary differences. Differences in attack-rates within ethnic groups according to occupational divisions, and within occupational divisions according to ethnic group, suggest that more than one factor is involved in the differences in susceptibility. There seems little doubt that among these factors the general level of socio-economic living standards plays an important rôle. Whether this is mediated by nutritional state, by hygiene, or by some general constitutional factor we cannot yet determine.

The demonstration of a decline in attack-rate with age requires comment. Such trends are often explicable in terms of specific immunity, but in this case the serological evidence does not accord with such an explanation. The fact that the outbreak was demonstrably attributable to a previously unknown virus also militates against the view that specific immunity played a part in determining differences in attack-rates. Cross-immunity between antigenic variants of influenza virus is unusual; yet it is difficult to imagine that so striking an age-trend is socio-economic in origin. It will be interesting to observe whether the age-trends in attack-rates found in the present study are repeated elsewhere.

Summary

An investigation is reported into the outbreak of influenza in Singapore during May. Attention is mainly confined to data from cases in the Singapore Naval Base.

298 patients were admitted to hospital. The mean duration of hospital stay was $5{\cdot}3 \pm 0{\cdot}24$ days. The duration of pyrexia in these cases was $2{\cdot}4 \pm 0{\cdot}87$ days, and the mean highest temperature recorded was 103·1°F. Every patient admitted had pyrexia. Apart from this the commonest symptoms were headache (193 cases), sore throat (135), and cough (93).

Complications were recorded in 39 cases (13%). These were seen chiefly in the old and in young children. Bronchitis (17 cases) and pneumonia (15 cases) were the more important complications.

Intervals between the medians of the daily distributions of cases among workers and dependants respectively suggested that the disease spread differently in the two groups. Clerical indoor workers had the lowest attack-rates. Together with the low attack-rates in the comparatively well-to-do Europeans, this suggests the importance of socio-economic factors in susceptibility to attack.

Serological studies on influenza patients as well as on those with other complaints showed that patients having influenza due to Singapore strain had had a greater exposure to other viruses in the past. Thus previous immunity does not explain differences in attack-rates.

We are indebted to the medical, nursing, dispensary, and clerical staff of the Naval Medical Officer of Health for coöperation in recording data. In particular we are indebted to Wardmaster Sub-Lieutenant O. A. Saunders, R.N., for much of the work of compiling data. Assistance in extracting data from hospital records was given by George Chia and Pedro Gasper.

We are also indebted to the Medical Director-General of the Royal Navy for permission to publish data from the Singapore Naval Base.

The Accident at Windscale

LAST week something happened in one of the nuclear reactors at the Atomic Energy Authority's plutonium factory at Windscale in Cumberland. The uranium in the reactor overheated and emergency measures had to be taken to cool it down. The situation was soon under control and first reports suggested that the mishap had not released any appreciable quantity of radioactive material over the surrounding countryside. On Saturday, however, samples of milk from cattle grazing on neighbouring farms were found to be contaminated with ^{131}I to six times the level laid down as permissible for long-continued fluid intake in persons occupationally exposed. The contaminating iodine has a half-life of eight days; so it was expected that the pollution of grass and therefore of milk would fall away rapidly in a few weeks. The consumption of milk contaminated to this extent was held to be harmless to adults unless continued for a long time.

But there was less certainty about the effect on children, whose milk consumption relative to body-weight is much greater, and as a temporary precaution the distribution of milk from farms in a coastal strip around Windscale, 7 miles long and 2 miles wide, was stopped. Farmers are to be fully compensated for the losses they sustain.

On Monday it became necessary to extend the area to 200 square miles around Windscale. The Atomic Energy Authority stated that this "further precautionary measure" was taken because "the measured level of radioactivity in milk samples, taken on a gradually increasing survey, has not fallen off as rapidly as was anticipated." [1] The area in which milk distribution has now been stopped extends eastward from Windscale to the foot of Wast Water, south-east to Torver, south to Greenodd, round Barrow and Millom, and back up the coast. There are about 500 farms in this area, but many of them are not commercial milk producers. Milk at present stored in churns on the farms is to be drained into the sea at the Milk Marketing Board's depot at Egremont, near Windscale.

The cause of this disturbing incident has not been made known; indeed, it may not yet have been determined. An inquiry into the circumstances is being held and nothing more will be said until it has been completed. The reactor was shut down at the time, so the episode was not caused by the reaction getting out of hand. The plant concerned was air-cooled, and the accident, it has been said, could have happened only in such a system. Filters trap only the particulate matter discharged up the plant's chimney, and the volatility of iodine would account for its escape past the filters. The announcement on Monday of the extension of the area of the milk ban suggests, however, that other contaminants of longer half-life, such as ^{89}Sr, may also have escaped. Measurements taken later this week should give a clearer picture of what is happening.

Influenza

In several Asian countries no cases of influenza are now being reported, and in Australia the incidence is decreasing; but the disease is appearing in Papua and New Guinea, which were previously free. In Europe and North and Central America the spread continues. In England, Wales, and Scotland the only regions where National Insurance claims have fallen are the East and West Ridings of Yorkshire; the national total rose to 540,896 in the week ended Oct. 1, compared with 408,379 the week before. In the 160 great towns of England and Wales, in the week ended Oct. 5 there were 442 deaths from influenza and 491 from pneumonia (the corresponding figures in the previous week were 282 and 418). 123 of the influenza deaths were of persons aged under 45. Of the children in London County Council schools, a quarter were absent at the beginning of the week.

In some countries (e.g., the Philippines) the death-rate has been high, chiefly because of complicating bacterial pneumonia. In its antigenic pattern the virus (A/Asia/57) is the most aberrant type reported since the discovery of the influenza virus in 1933. For this reason populations have little resistance, and the disease spreads rapidly. In Holland, the United States, and Australia antibodies to the "new" virus have been found in persons aged 70 or more; the present pandemic may be related to that of 1889. Vaccines prepared from the virus stimulate little antibody, at least after a single dose. Experiments are in progress to prepare an attenuated live-virus vaccine; in the Soviet Union virus, after passage through egg, tissue-culture, and egg, has been sprayed into the

1. *Times*, Oct. 15.

nose. This method of immunisation may cause a mild attack of influenza, and its efficacy, according to W.H.O.,[1] is questionable.

Poliomyelitis

Notifications of poliomyelitis in the week ended Oct. 5 totalled 116 (124), comprising 87 (87) paralytic and 29 (37) non-paralytic (previous week's figures in parentheses). The median total for the corresponding week in the years 1948–56 was 155. The total number of cases up to the end of the fortieth week was 4655—the third highest total in 1948–57.

Negotiations for the purchase of Canadian Salk vaccine are complete, and a batch for testing has already arrived. Negotiations with an American firm continue.

According to the Ministry of Health, enough vaccine will be purchased for vaccination to be offered to all children under 15 and to all expectant mothers. It is expected that safety-testing will not be complete until the end of the year, and vaccinations will have to be concentrated into the first six months of next year.

Points of View

TOWARDS A PHILOSOPHY OF SOCIAL CARE

FLORA BECK
A.M.I.A.

OVER the past fifty years or so the basis of social work has changed. Needs and knowledge have altered, though public opinion has been left to follow at a limping rate. At the turn of the century few women elected to become social workers, but those who did were firm in their convictions and they left others in no doubt of what they were about. Today the number of social workers is much greater, but the definition of social work varies from one speaker to the next, while the public remains vague and sometimes uneasy about what social workers do.

* * *

A principle which must underlie all effective social care is that each separate individual is unique, and uniquely matters. There is no reason to pretend that all men are equal; and few would seriously wish that the mansions of the spirit should be built out of a dull conformity of barrack brick. What is needful is to accept as an article of faith that every single living person, of whatever age, sex, colour, race, or creed has the right to be considered and respected as an individual.

But respect for life and a warm wish to encourage the fullness of life in all its varied forms does in itself impose a discipline. Intent concern for the individual means that no one individual's interests can be pushed at the expense of all others. The social worker who says, and means, that the happiness of one known down-at-heel half-caste illegitimate errand-boy is of as much account as the happiness of anybody in the land, does not for that reason plunge into sentimental feeling and rash activity on his behalf. In deciding to what extent the boy should be helped, the needs of others and the resources available must be taken into account. It is true sometimes that little can be done. It is intolerable only if no-one cares.

The confidence of society depends on each person in it having good reason to believe that some representative of authority would personally care what happened if he were in danger or distress. The administrator, numbed by the sheer mass of a national problem, may easily lose sight of this. On one hand the demand of needs, needs, needs, needs is as deafening as the cry of a million wide-beaked starlings in the nest. On the other there is the sight of ever dwindling resources. He feels he should say No. He knows the clamour will rise to crescendo if he does. He grows weary and disillusioned, feels that too much is asked, too much taken for granted, even at last that it was wrong to have begun to give at all. Perhaps it was, if the wrong thing were given first; but like as not it was not so much what was given as the manner of giving that was wrong.

* * *

It is reasonable to claim that the Welfare State is one of the most worthwhile social experiments of the century. It would certainly be wrong to denigrate or to deny the solid benefits which it has brought. It would be equally wrong to pretend that it is faultless, or that it has worked out entirely as was expected. A centenarian looking at the country now might say that people are better off than they have ever been before and further still from being satisfied. This seeming paradox is baffling to those who tend to look at social problems in the mass. Looked at more closely it is understandable. The Welfare State has made a helpful attempt to cure what had been a seriously sick society. On its own large scale it has discovered one of the pitfalls that individual social work, after long years of trial and much error, is learning to avoid.

When members of the community are found to be in dire straits, the obvious solution seems to be to give them the material help they need. This is the easiest, quickest, and most comforting action for the giver. Sensitive people who have enjoyed the security of good income, good housing, and good opportunities in life must feel troubled by close contact with others who lack these things. Conscience whispers: who are you and what have you done to deserve to be so much better off than they are? Uneasy self finds quick relief in giving. In casting out an excess balance of material goods, the load of guilt is lessened too. All this is natural, and there is nothing wrong with it except if it should happen blindly and so defeat its good intent.

A healthy-minded person, well equipped with provisions, who finds a destitute child will feel a natural desire to give it food. But if he is experienced and humane, concern for the child's needs will curb and direct the desire to help. To give food too quickly to a hungry child and then to spurn it as an unpleasing brat because it is sick all over you reflects more discredit on the giver than on the child. Where adults have been reduced to helpless dependence this applies no less. To overfeed a starving man and then, when he gets ill, to say that it proves that he did not need food, betrays ignorance of physiology.

Social disorders are not cured overnight by handing out dollops of prosperity. Their long-term results need careful treatment based on close study and an unafraid concern. At the individual level, experience in social casework has taught that to give material help to a family in serious need may, by itself, do more harm than good. Before attempting to give long-term treatment it is important to find out how and why the situation arose and also to discover what harm it has already done to the feelings and initiative of the persons concerned. To shower goods before fanning back the sparks of social life may be like emptying a bucket of coals on to a dying fire and then wondering why it goes out. A good deal is already known about the theory and practice of treating individual social breakdowns, and it is important that this knowledge should be made more freely available, since it has close relevance to wider issues. The scale of present-day social and industrial organisation makes it more, not less, important to understand the reactions of individual human beings.

1. Press release W.H.O./50, Sept. 27, 1957.

It is often necessary to legislate for or to negotiate with a group; but that group is less than the sum of its individual members. The feeling that holds it together as an entity cannot match the intensity and volume of feeling that could be released within one member of it by a stimulus that reached the central core of his most personal emotions. A reaction of this kind in one individual may set off similar reactions in others around him, and when this happens strong and sometimes violently irrational group-reactions take place. When a large proportion of individuals in any group or class lack the feeling that they belong to or matter to the society in which they live, hostile and destructive explosions of feeling are likely to occur. Among such sections of a population it becomes progressively more difficult to evoke any positive contribution to social life, and creative activity drops to a low ebb. An improvement in material standards of living may lessen the risk of explosion without curing the social disorder. Money then becomes a major drug of addiction and happiness is hard to find.

* * *

It is often easier to see the road ahead if we look back along the way we have come. The depression between the two great wars nurtured the ideas out of which our social legislation has grown. That depression was in itself a large-scale example of an economic disorder that had been endemic in this and other countries since the beginning of the industrial revolution. The social ills it worsened had been known for centuries. Its size and severity was such, however, that it produced a kind of social damage that is like lowered vitality after a long illness. An obvious catastrophe would have done less harm. If a tidal wave had engulfed a large part of the country, the rest of the population would have been instantly concerned, active, and eager to help survivors. The shock of the disaster would have been offset for many by the warm glow of discovering that they belonged to a human and humane community.

Economic depression made less obvious but no less serious inroads, affecting first the levels of society where social conditions were already poor, and spreading to include large areas of the country where life became stagnant and an embittered apathy did more harm than physical deprivations by themselves could ever have done. There seemed no end to it, and it was useless to hope that anything would ever be done when no-one cared. That was how it looked from within. In fact some people did care deeply, but not enough of them to provoke a healthy, nation-wide response. Many people had no idea what life in the so-called distressed areas was like, and many more tried to shut out the knowledge. Some even denied the facts and seized on any excuse, real or imagined, to run down "the unemployed" as a worthless, undeserving lot. Conscience was uneasy, and this was a natural reaction. It is no use now to blame people for what they had at the time neither the strength to accept nor the wit to understand. The fact remains that the harm done to social confidence and morale during that period destroyed much that still remained of an earlier and more robust tradition; and the damage has yet to be repaired.

Some of the mistakes made at the time were inevitable. Most would have been forgiven, and many hardships could have been endured without lasting bitterness if it had been made plain by person-to-person contact that those in authority knew and cared what the unemployed were having to endure. In fact usually the reverse happened. Some monetary relief had to be given; the size of the problem and a fear of relief being "abused" influenced the regulations, and these were interpreted and applied by clerks and minor bureaucrats who had no training and no responsibility for a full programme of social care. Actions based on fear sometimes cause the ills they seek to escape. A tendency to trade on gullible givers, to get as much and to do as little as possible, is a common symptom among people who have lost or never learned the pleasures and satisfaction of becoming responsible and valued adult members of the community. Nothing is so destructive to the dignity of a man as the need to accept money. The miseries of the dole, the humiliating way in which the means test was applied scarred the self-respect of men who could have had the finest influence on their own generation of industrial workers and on the next.

* * *

The Welfare State legislation was designed to abolish these miseries of the past. The Beveridge report, on which it was based, was produced at the request of a Coalition Government in 1942 at a time when the nation had seemingly recovered full vigour and sense of unity. The perils and challenge of a world at war provided the vital stimulus, and people achieved prodigies of self-help and mutual support. All, with sad exceptions among helpless aged folk, were given a new sense of value. There was work and to spare for every able-bodied person; even the disabled were now worth training. Children, though unproductive, were specially precious because they symbolised the future we were fighting for. The war provided what had been absent during the depression—a tangible external foe, a common danger, a comradeship in adversity that broke through class barriers, and visible proof that authority cared about the sufferings even of the poorest.

* * *

With peace reaction came. When there was no longer an outside enemy, the pressure of old grievances was felt again, and the sectional distrust of earlier years seeped back. Younger workers were encouraged to use the weapon of new bargaining-power, and they have freely done so; sometimes to the chagrin of their elders, who see them accept too glibly as a kind of natural bounty their new standard of living—careless of those who laboured so much harder for much less. Many who hoped in their youth that they might live to see this day, find themselves in old age as poorly off as they have ever been. The young, for all their money, still feel poor.

There is a tendency to argue that the Welfare State has somehow been to blame. The idea behind it had been different from what is commonly imagined now. One of the chief aims of the social insurance scheme outlined in the Beveridge report had been to reduce National Assistance to a dwindling minimum. Insurance benefits and pensions were meant to guarantee a bare subsistence, leaving people free by saving or voluntary insurance to raise the level nearer to the standard of living they desired. The problems of how to gain popular support for this austere concept deserved serious study. It was not to be assumed that the thrifty habits of the best workers in a more settled age would necessarily be seeded into a post-war generation. It was still less likely that these personal qualities could be grafted by chance on to a Government-sponsored scheme. And yet, fairly faced, it was a challenge that the people might have met.

Insurance cannot secure the barest level of subsistence if balance is upset by seesaw rising costs and rising wages. The supplementing of insurance benefits by National Assistance, with inevitable means test and dead-levelling results, has become a matter of routine. Much has to be done elsewhere before we can alter that. The focus of our economic ills has shifted: poverty has become a national rather than a personal disease. The main trouble has been an attempt to distribute more than the national purse contains. With financial stability undermined, workers have become like men trying to escape from a quicksand by climbing on to one another's shoulders.

In days gone by, many able and educated men convinced themselves of their right to force the workers' wages down and live in luxury themselves. Now the situation has changed, we need feel no surprise if men with less education and experience show the same kind of human weakness.

We have had the good fortune to achieve a major social revolution without bloodshed. There are tremendous opportunities ahead which will be lost if we become swamped in a tide of disillusion. Once society loses confidence in human nature, anxiety infects the old and young, augmenting equally the lawless violence of youth and the reactionary counter-violence of authority. The need now is to provide a peace-time stimulus that will evoke qualities of endurance, comradeship, and creative effort similar to those that can be released under the stress of war. This requires imaginative leadership, freely followed. For leadership to be trusted and accepted, confidence must be built up. This means the confidence of separate individual human beings—people who can each believe that the self-discipline and efforts asked from them are reasonable, who feel that their own point of view is understood and valued, who know and accept with pride and tolerance that those in authority are of the same imperfect flesh and blood as themselves. Until this can be achieved, the positive ideal of a subsistence below which no-one need fall gives way to the negative limit of a dead level above which no-one may rise.

* * *

Social workers are not directly concerned with political leadership, with industrial management, or with any form of authority. Their freedom from this responsibility is essential to the proper practice of their profession. Though they may in varying degrees act as agents of authority, they never constitute authority in themselves. Their responsibility is to the individual, a person whose uniqueness and human value must be respected whether he is in conflict with authority or not. This responsibility to the individual needs to extend in both directions. Constructive care and understanding for the individual who finds it hard to accept authority is not a sufficient social service unless the same consideration is shown to the individual in whom authority is vested. It is humanly no less hard to meet the demands of society at the apex of the pyramid, and where the weight of responsibility is greatest, the need for understanding and support is greater too. A social worker who considered himself the champion of the underprivileged would be in danger of setting a greater human value on, say, a victim of National Assistance Board entanglement than on the official who misapplied the Act or the Minister responsible for that Department. But the official and the Minister have an equal right to be considered as human beings, and righting a wrong is not an act in their despite, but an action that is in the interests of all concerned. It is to the harm and discredit of the official that he should lack, or be thought to lack, a sense of justice or humanity; it is to the harm and discredit of the Minister that real or seeming injustice should be done in his name. The picture may look different from the other side, and it is in two-way interpretation, back and forth, that social workers have a special part to play in promoting the confidence on which democracy depends. The social worker has opportunity to study the difficulties of individuals in relation to authority and to know what approach is most likely to evoke spontaneous self-help, coöperation, and acceptance of hard realities. While feeding the essentials of this back to the powers that be, he can also gain enough knowledge of their point of view to interpret to the public the practical and the human difficulties that beset authority.

A State which aims to have free, live, and individual citizens and to care for them in distress need not be a bureaucracy: indeed, it defeats its own end in so far as it becomes one. Who ever felt warm personal feeling for a penny-in-the-slot machine? So long as it works, people take it for granted; and when it gets out of order they shake it or hit it or just walk away. People get to feel like that about the Welfare State when it is not recognisably human in its impact. It does not have to be perfect, but it must be alive and it must care—otherwise its beneficiaries will take out of it as much as possible and give back less than nothing in return. The attitude and outlook of the people who administer the public services, their respect and understanding of the views and feelings of those they serve, the respect they command by their own quality as human beings, is of immense importance to our whole economy. If they have such stature in themselves that they can afford to treat their humblest client as an equal, the pride and affection of the people will be roused to do them credit.

Relief and prevention of distress, whether of mind, body, or estate, is a part and not the whole of social care. The knowledge and skills of social work should never be used as a tool for adjusting people to a dull conformity. The greater the skills available, the more sure must we be of our intent. Our aim should be to achieve fullness of living for every person, with flexibility great enough to cover occasional extreme eccentricity of individual choice, with opportunities to develop loyalty, and with a will to tolerate such restrictions as are needful to society as a whole. The State exists to preserve life for the people, not to drain life from them.

Symposia

EVALUATION OF DRUG TOXICITY

A SYMPOSIUM, sponsored by the Pharmaceuticals Division of Imperial Chemical Industries, Ltd., was held at the new research laboratories of the division at Alderley Park, Cheshire, on Oct. 3 and 4.

Toxicity in Clinical Practice

Prof. E. J. WAYNE (Glasgow) said that a large enough dose of almost any drug would cause untoward effects, related either to its main action or to its side-effects. The therapeutic index was some guide to these hazards but was not easy to arrive at in man. The estimated figures of 15 for morphine, 20 for the barbiturates, and 100 for atropine indicated only the greater margin of safety with the last of these. The commonest toxic effects in man arose from exaggeration of unwanted side-effects (e.g., drowsiness with anti-histamines). These could often be counteracted by a second drug given at the same time, but a better course was to attempt to synthesise new or related compounds relatively free from undesired side-effects. In this way substitutes for atropine had been found with improved properties, but the best of these was still far short of the ideal.

Less common but more serious were those toxic reactions involving an abnormal and often allergic response. Skin, bone-marrow, and liver were mainly affected, but asthma or acute allergic shock might occur. The tendency of a drug to cause sensitisation phenomena was largely unpredictable, but certain chemical groupings (e.g., the "benzamine" and quinonediimine structures) were often involved. The incidence of such reactions was difficult to estimate even with drugs in common use. Phenylethylhydantoin ('Nirvanol'), formerly used for chorea, produced signs of sensitisation in over 90% of patients; with chloramphenicol the incidence of blood dyscrasias was estimated at between 1 in 10,000 and 1 in 100,000. The risk had to be balanced against the patient's need. Only clinical experience with a drug could reveal these dangers—and then only when it had been in use for some time.

Differential Toxicity

Dr. E. WESTON HURST (Alderley Park) reviewed the differential toxicity of certain drugs for male and female animals—a matter of some moment to those engaged in toxicity tests of new therapeutic agents. The differential might be small, as with novarsenobenzene, to which the female mouse was only 10% more susceptible than the male; but chloroform, which was safe as a general anæsthetic for female mice, caused fatal renal necrosis in minute concentrations in male mice of certain strains. Either of the sexes might be the more susceptible, even within a group of closely related compounds, and commonly a differential had been observed in only one species. Generally speaking it developed only with sexual maturity, and in most adequately studied examples was under hormonal control. Gonadectomy might abolish it, while the administration of sex hormones to intact or gonadectomised animals tended to direct the recipient towards the state of resistance or susceptibility associated with the hormonal status simulated. The precise mechanisms mediating these sexual differences had seldom been approximately defined; but certainly in some instances the metabolism of a drug, under hormonal control, to products differing from it in toxicity was involved. Dr. Hurst described two instances, under investigation in his laboratory, of the influence of sex on therapeutic action. The first concerned the prophylactic treatment of equine encephalomyelitis in the mouse with mepacrine, the second the effect of streptomycin on a streptococcal infection in mice. In neither was the difference in response between the sexes accounted for by a difference in susceptibility to the infection.

The Histopathologist's Role

Dr. G. E. PAGET (Alderley Park) emphasised that experiments for pathological evaluation must be planned with this end in view from the start. The levels of dosage of a compound given should include the maximum tolerated, dosing should continue for six to eight weeks, and untreated controls should always be run. At necropsy an adequate range of tissues should be taken, immediately fixed, and processed critically, routine methods being freely supplemented by modern histochemical and biophysical techniques. Toxic effects causing peculiar concern were those on the gonads and carcinogenic effects, and steps should be taken to ensure their detection. For carcinogenicity this would entail special long-term tests.

Since the effects of a substance in man could never be predicted certainly from the results in other species, the "least favoured species" policy should be adopted in making the extrapolation. Consideration should also be given to the seriousness of the lesions seen in the laboratory animal, with reference to their reversibility in man and ease of clinical detection. This approach might result in the rejection of compounds which would prove perfectly innocuous in man were they tried, but in the absence of certainty some risks ought not to be taken.

General Principles of Assessment

Dr. J. T. LITCHFIELD (New York) said that, for the evaluation of desirable and undesirable properties in chemical substances, efficient procedures could be designed if we assumed all substances to possess in some degree the property of concern to us, and proceeded stepwise in terms of a definition of the extent of our concern. In screening large numbers of essentially unselected compounds for some desirable property, "interesting" activity might be defined as that exceeding some predetermined value greater than the effect of physiological saline. We could then design a test to sort all substances into the classes "interesting" or "not interesting". The resulting test would be qualitative, but by the use of exact statistical procedures could be designed so as to be of the greatest economy for the degree of interest and likelihood of error in decisions specified. The next step was to determine "how interesting", and for this a study of dose-effect relationships and comparison with known standards was required.

Applied to the evaluation of an undesirable property in a drug these principles again involved the definition, in relation to a well-defined standard, of a value at which activity became "interesting". For carcinogenic action this might be defined as activity substantially greater than that of food alone which, on good evidence, behaved experimentally as if it were a carcinogen. This approach would avoid fruitless efforts to prove the complete absence of carcinogenic activity.

Inter-species Differences

Dr. J. M. BARNES (Carshalton) referred to differences between species in their response to the administration of certain chemicals and the possibility of unexpected toxicity appearing when a new drug was first given to man. Partial solution of the latter difficulty lay in extending tests to a wider variety of species; but fuller understanding of these differences would come only with fuller knowledge of comparative physiology and biochemistry. Selective toxicity, he thought, must be closely linked with metabolism. A drug might be metabolised to a different extent in different species to products more or less toxic than itself. Mammalian liver-cells contained a system, studied extensively by Brodie, which was remarkably versatile in effecting various metabolic transformations in chemicals foreign to the body. The livers of various species differed in this capacity; that of human liver cells had still to be explored. The capacity of other tissues, especially kidney and brain, to cope with foreign chemicals that reached them should be investigated along similar lines. In intact animals early warning of toxic action on the brain was sometimes given by minor behavioural changes detectable only by close observation.

Determinations of the $L.D._{50}$, though useful, required uniformity in the test animals. Perhaps laboratory stocks of rats and mice had become too uniform for the detection of idiosyncratic reactions, even if very large numbers were used. Perhaps the best safeguard against unexpected reactions of this type lay in fundamental study of such examples as were known to occur.

Allergic Reactions

Mr. G. E. DAVIES (Alderley Park), discussing allergic reactions as hazards in the use of new drugs, classified these as immediate (such as urticaria), delayed (such as contact dermatitis), and blood dyscrasias. The ultimate solution of this problem depended on developments in the production with small molecules of allergies in animals. This had been achieved only, as in the classical studies of Landsteiner and his associates, with *reactive* chemicals, and thanks to those researches the main steps in the development of contact dermatitis now seemed clear. The chemical penetrated into cells and there conjugated with a protein, the complete antigen so formed acting as a stimulus to the production of antibodies which remained attached to the cells or were transferred to similar cells. Drugs were not in general highly reactive, and the claims to have produced allergies with them in animals were unconvincing. Pertinent questions were how drugs did, in fact, become complete antigens in certain individuals, and why once having done so, not necessarily on their first exhibition, they continued to do so thereafter. Reactive metabolic products of drugs might be suspected as the immediate precursors of antigenic protein-containing conjugates. The conditions for their formation might occur only in certain individuals, arising in them by somatic mutation or induced enzyme activity only after a certain time. These speculations opened up various possible approaches to the production of true drug allergies in laboratory animals.

Toxic Action on Hæmopoietic System

Dr. W. JACOBSON (Cambridge) said that as both red and white cells had a limited life-span their replacement required frequent multiplication and subsequent maturation of the precursor cells. In consequence toxic action here resulted in a varied pattern of response. Direct or indirect interference with cell multiplication or toxic or lethal action on the immature cells would result in depletion of the type of cell affected. On the other hand destruction of circulating mature cells would lead to compensatory activity in the bone-marrow going on to hyperplasia or perhaps to malignant change. Little was known about the mechanism by which many substances exerted their toxic action on the bone-marrow. It was known, however, that folic-acid antagonists could arrest cell division in the precursors of normal and leukæmic white cells by competing for folinic acid, which is required for several stages of the biogenesis of nucleic acids; they could also interfere directly with division in these precursors in another way. The cells of acute leukæmia, but not normal leucocytes, could inactivate these antagonists and remove their inhibitory action. In recent experiments he had shown that leukæmic cells could both build up their own folinic acid from a suitable pteridine and synthesise a folinic-acid antagonist from an abnormal pteridine. Normal cells could not do either.

Hepatotoxic Substances

Dr. P. N. MAGEE (Carshalton) described attempts in the M.R.C. Toxicological Unit to elucidate the initial "biochemical lesion" involved in the action of selectively hepatotoxic substances in the rat. A single dose, for example, of dimethylnitrosamine would produce acute liver necrosis from which, if the animal survived, the liver recovered completely. Chronic dosing caused necrosis and regenerative hyperplasia and might lead to the appearance of liver tumours. These were common patterns of response to liver poisons. Using a calorimetric method of measuring liver blood-flow in rats with a closed abdomen, Stoner had shown that the initial effect of dimethylnitrosamine (or of carbon tetrachloride) was unlikely to be due to ischæmia. Other evidence also favoured a direct action on liver-cells, probably by way of interference with protein synthesis at cytoplasmic sites. A toxic metabolite of the liver poison might be implicated. The essential problem was to distinguish the primary reaction between the toxic molecule and an essential cell constituent from changes which occur only as part of the process of cell death.

The behaviour of certain pyrrolizidine (senecio) alkaloids (e.g., lasiocarpine) was unusual in that single doses could produce chronic and apparently progressive liver lesions which became clinically manifest only weeks or months later. The eating of plants containing these alkaloids caused liver disease in cattle; their consumption in "bush teas" had been suggested as an ætiological factor in human veno-occlusive disease.

Dr. K. R. REES (London) described some joint experiments with J. D. Judah on the action of liver poisons on structural components of liver cells. Observations in acute liver injury and during the induction of cholangioma, both brought about by giving thioacetamide, revealed a striking increase in size of the liver-cell nuclei and nucleoli and in the ribosenucleic-acid (R.N.A.) content and R.N.A./protein ratio in these cells. Respiration was depressed in the isolated mitochondria, and accumulations of calcium and citrate, prevented by anti-histamines, occurred in the liver.

In other studies they had shown that pre-treatment with metal chelating agents depressed respiration in mitochondria isolated from the brain. It increased the sensitivity of the system to copper, and its effect was reversed by cobalt and nickel but not by other metals or by vitamin B_{12}.

The full proceedings are to be published soon.

In England Now

A Running Commentary by Peripatetic Correspondents

As an examiner the University of London is on the grandmotherly side. With sinking heart we once again gathered together all those silly bits of paper, as we had done so many times before. Armed with Treasurer's Slip (please print clearly), Application Form, Cheque (crossed Westminster Bank, Russell Square Branch), various certificates, envelopes by the row (candidate must apply stamp) addressed in our own somehow weirdly unreal writing to ourselves (block letters), and a special red one if we wished to be present at some remote ceremony for successful candidates, we staggered down to the nearest post-office to demand a registered envelope, size K. Our tiny local office had run out already: "Really dear," said the postmistress kindly, diagnosing our pre-examination neurosis at a glance: "Don't know why they bother with all this; after all we can register any envelope, but there it is." And there it was, or rather wasn't, and she had to rummage about underneath, finally unearthing a pseudo-size K marked "Overseas" which she industriously scribbled out inking "Inland" over it. "There," she said: "That should be all right, but I'll have to put 9*d*. more stamps on it." It appeared that overseas registered post for size K, whether to Djakarta or Vladivostok, costs 9*d*. *less* than sending the thing five miles up the Old Kent Road via the Elephant to Aldwych and Kingsway, and finally the Senate House. Post early for Examinations via Beirut and Save Money.

Now at dear old Queen Square they are a much more down-to-earth lot. Write the cheque on the back of a cigarette packet for all they care as long as it doesn't bounce, or send the fee in 3*d*. pieces in a large sack. They couldn't care less whether you register the letter or not, and they are more adult over their exams too, in an informal and gentlemanly way: not for them solemn threats about Writing on the Blotting Paper and Including All Rough Work in the Answer Book. Up the Conjoint Board! But they jolly well fail you just the same.

* * *

Earlier this year we bought ourselves a new bed. The step was not lightly taken. We occupied some hours of salesmen's time, nodding with bucolic incomprehension as we heard of the modern wonders of foam and interior-sprung mattresses. Finally our choice fell on a splendid-looking 'Sleep-if-you-Can.' We were invited to recline on it; but in an emporium this seemed hardly decorous, so I bounced my rump once or twice on the edge and pronounced knowingly: "Excellent."

Three months have passed. They seem more like six—as indeed they might, for the normal sixteen waking hours of the twenty-four have been augmented by at least six sleep-free hours at night, six obstinately wakeful hours despite the best efforts of the drug industry. Yesterday our appeal was answered by a visit from the shop's bed expert. My wife asked shyly whether he often dealt with similar complaints. Why, yes, he said. Only the other day he had dealt with such a complaint. He'd had no trouble in detecting the cause. The couple had thought that they could move on to a firm modern mattress from a feather bed. A *feather* bed! Here the expert threw back his head and laughed merrily at the recollection. Then he pulled himself up. We hadn't been sleeping on a feather bed? No? That was good. The expert turned next to psychogenic factors ("I don't want to seem impertinent, but . . ."). Having cleared the ground here, he turned to physical causes with the relief of the clinician who sees psychology as a usurper. The mattress cover, the pillows, the mattress itself—each in turn was declared up to specification. But why was the bed like a concrete slab? Well, we must persevere, and wear it in: it would soften in time. My wife took him to the children's room, which has two divans—part of a job lot bought for a fiver each. Why, she asked, had these been comfortable from the start? Cheap stuff, said the expert, his lip curling: wouldn't last. But, countered my wife, our children had long been known for their untender consideration for beds; and these were

as good as ever. Now one-up, my wife led the expert to our spare room. Here, she said, were two pre-war beds with interior-sprung mattresses. Why, she asked, could beds not now be made soft like these? The man felt the beds and stepped back, his face aghast. Did she not know—and she a doctor's wife—that mattresses were not made to sink into but to support our frames so that our trunks and limbs should be undistorted? But, said my wife, in our senescence orthopædic considerations were secondary to the search for sleep.

This informal exchange of views, this symposium (timed by our daily), lasted from 9.35 A.M. to 11.15 A.M. The expert took his leave with cordial expressions of good will and a promise to convey our sentiments to the manufacturers. There the matter rests. If meanwhile, anyone would care to make an offer for an expensive, scientifically constructed bed that's hardly been slept in . . .

* * *

"I think he is a P.A.," wrote my junior colleague, "but I will get his absolute values done." I hoped that the recipient of this letter would not be one of the well-educated elderly general practitioners who sometimes take me to see their patients. He would be shocked to think that a man could be a disease, and might not even know what the abbreviation stood for. Should he decide to interpret the jargon, however, I think his worst shock would come when he found that the ratio between two somewhat inaccurate measurements had become dignified with the name of an Absolute Value.

* * *

Your projected change in format has struck dismay into the hearts of at least two regular readers. It is almost as though *The Times* were to relegate its calm, unruffled, and most soothing columns to some hidden corner of its interior; we would have to *open* and *refold* its sheets to read the hatched, matched, and dispatched or to savour the intimacy of the personal column, and in the meantime our eyes would already have been assailed by glaring headlines. We see equal danger in the new *Lancet*. Who can deny the sedative, tranquillising value of our old cover? Each week almost the same, but not quite. How we loved to look for the familiar advertisement of *The Lancet's* own publications. Was our own favourite text-book there? Dear me! A new edition of Sunk and Carful's *Surgery*. The sixteenth! Now ours would be about the eighth, when old Sir What's-his-name was editor. When did he die? Thus lulled into sweet reminiscence we pass on to our second cup of coffee before steeling ourselves to turn over the page to inspect the Contents. Imagine their impact now, unfamiliar and challenging, unbearably informative before we have dallied over our cover. We shall be forced to open and hunt for our soporific; perhaps even pass through vaccines and drugs before we find the tasteful array of approved academic publications. No! Definitely the front page is not the place for the table of contents.

* * *

The influenzal epidemic was taking its toll of nurses, and the medical registrar was away. I approached two anæsthetic registrars and asked their help in keeping an eye on the nurses until more regular arrangements could be made. After due thought they each gave the same reason for being unable to cooperate—they did not feel competent to deal with this type of problem.

I hope that this was due to false modesty; but, if not, I can only say that I should prefer to be anæsthetised by a real doctor.

* * *

Phenobarb., Oblivon,
Bless the bed that I lie on.

Four capsules by my bed,
Blue and white and green and red.
One alone's no use at all,
Two will send me up the wall,
Three should bring a night's repose,
Four will make me comatose——

Phenobarb., Oblivon,
Bless the bed that I lie on.

Letters to the Editor

"PNEUMOCONIOTIC NEUROSIS"

SIR,—I am pleased indeed to hear that in Dr. Holt's area (Oct. 12) each claimant for pneumoconiosis benefit has a full clinical examination and an exercise-tolerance test in addition to X-ray examination; I should be still more pleased if he—or anyone else—could confirm that this sensible practice is in operation throughout the country. Respiratory-function tests are surely essential in any modern assessment of respiratory disability.

I cannot share Dr. Holt's view that "within the margin of human error the present system seems to have been the best devised." In South Africa similar regulations have been scrapped and a completely new approach made: assessment is made on the basis of a full radiological and clinical examination, with respiratory-function tests in every case, and is also related to the length of time a man has worked underground—a functional and practical method which allows the medical profession to make a reasonable interpretation on the basis of observed factual data instead of demanding specific answers to posed legal questions which no human agency can satisfy.

I agree entirely that severe respiratory disablement in miners is often the result of bronchitis and emphysema rather than pneumoconiosis. Far from ignoring the fact, this was the group I had in mind when I mentioned "men with severe respiratory disablement who have worked in the pits for years," and who at present have not the slightest chance of being considered eligible despite the thousands of shifts they have worked underground in a confined atmosphere in the dirtiest and dustiest of all occupations. Does anyone seriously doubt that this occupation is an important factor contributing to their disability, even if their X-rays show no evidence whatever of pneumoconiosis as such? The incidence of bronchitis and emphysema amongst miners speaks for itself. Smoking and infection are other factors; but, as nearly half their waking day is spent underground, miners on the whole smoke *less* than the average—hence their lower incidence of bronchial carcinoma. Prolonged exposure to dust is the *main* responsible agent. In South Africa the absurdity of ignoring the obvious has been admitted and "pulmonary disability" is the criterion on which claims are now assessed. Might we not at least consider doing the same? And is it not time that the whole position were reviewed in the light of recent knowledge?

Clare Hall Hospital,
South Mimms, Barnet. NORMAN MACDONALD.

ESTIMATION OF PLASMA PROTHROMBIN

SIR,—Your leading article of Oct. 5 was most gratifying since it expressed lucidly the desirability and need for a carefully standardised technique to carry out the prothrombin-time test.

What is true of the prothrombin-time holds equally well for the other tests employed in hæmatological research. Progress is best achieved when the various investigators can understand the results obtained by their fellow scientists. To that end an international committee has been organised to study the problem of nomenclature of the clotting factors. One of the serious difficulties the committee encounters is the evaluation of experimental data offered for the establishment of a new clotting factor or bleeding state, because the methods carried out in one laboratory may differ greatly from those of another, as illustrated by the variety of normal ranges found in even as simple a test as the clotting-time of venous blood.

Obviously, real progress in the problem of standardising technique cannot be achieved by any individual

or committee by arbitrary means. The solution can come only from a slow evolution, with a blending of theory and practical experience. Most investigators will agree that the principal objectives of the tests used in hæmostatic studies are: (1) to establish the existence of a coagulation defect; (2) to identify the defect; (3) to measure it quantitatively; and (4) to determine the corrective action of therapy. The procedures most commonly employed at present in clinical or hospital laboratories are the clotting-time, bleeding-time, tourniquet test, platelet-count, prothrombin-time, thromboplastin-generation test, and the prothrombin-consumption time. Perhaps a good beginning would be to concentrate attention on these tests and to base the standardisation of technique on how satisfactorily the four stated objectives are met.

Marquette University,
Milwaukee, Wisconsin. ARMAND J. QUICK.

SIR,—I would like to comment on Dr. Toohey's letter last week. He states that saline brain emulsions should be used as a source of thromboplastin, because they are easier to prepare than acetone-dried extracts, and they give a more constantly reproducible activity. This implies that otherwise the two preparations give similar results. I feel it should be more widely appreciated that variations in the method of preparing thromboplastin give different results. Several workers have demonstrated this.

In a recent paper,[1] I showed that when the test for prothrombin efficiency was performed as described by Dr. Toohey,[2] plasmas gave consistently and appreciably higher ratios than when performed using a modification of Quick's original method in which acetone-dried brain is the source of thromboplastin.[3] Thus, ratios within the range 1·5–2·5, obtained using Quick's method, corresponded to ratios in the range of 2·1–3·6, using Toohey's method. The difference became progressively greater as the ratio increased, so that the "hæmorrhagic level" is at a much higher ratio if Toohey's method is used.

In this investigation I was not concerned to show that one method is "better" than another (although, in fact, in the course of it I found that both gave equally reproducible results), but what I wish to emphasise is that they give different results. In practice this means that a clinician dependent on a laboratory using Toohey's method should aim to keep the prothrombin ratio at a higher level than if Quick's method were in use.

Finally, the unqualified statement that saline brain extracts keep "absolutely stable for an indefinite period when stored at −20°C" is contrary to what is found in practice.

Institute of Pathology,
The Royal Infirmary,
Cardiff. D. E. B. POWELL.

OLIVER ST. JOHN GOGARTY

SIR,—Your obituary of Gogarty suggested that no student of the Meath Hospital, Dublin, of thirty years ago would remember what Gogarty did for that hospital. This statement must surely have been meant to be provocative. Here is one student who was dresser to Gogarty in the turbulent times soon after the episode of the "presentation of swans," and soon after Gogarty's return from his brief sojourn in Harley Street. On many occasions when scrubbing-up, standing in his splendid silk shirtsleeves, he would talk in witty words which were sheer joy to hear. On one occasion before we scrubbed-up together, he handed me a poem which he had written that morning before coming to the hospital. I have the poem to this day.

No mention was made in your obituary of Gogarty's interest in the early days of private flying in Ireland about which he liked to talk. The term "colourful character" has been used to describe people who interest and entertain. Gogarty was in his attitude to life rather like that other Oliver "who wrote like an angel." Here is one former student of his who was fortunate to have sat at his feet, and who is all the richer for having known Oliver St. John Gogarty and is aware of the debt the Meath Hospital, Dublin, owes to him.

R. G. F.

INFLUENZA

SIR,—During the past years I have found post mortem that infants who were diagnosed by the practitioners in attendance as having suffered from influenza and died suddenly thereafter, gave on bacteriological examination of their lung tissue an invariably pure growth of *Hæmophilus influenzæ*. This organism has become more dominant of late and one is frequently recovering it in pure culture from elderly bronchopneumonic patients, from the pneumonias and meningitis of infancy, and in cases of suppurative sinusitis. Unless this organism is looked for routinely, its significance cannot be truthfully but only adversely assessed.

Department of Pathology,
General Hospital,
Northampton. R. M. HEGGIE.

PELVIC TUBERCULOSIS AND HIRSUTISM

SIR,—During the past two years I have observed that three patients with gross hirsutism had pelvic tuberculosis of a mild and almost unsymptomatic variety. It was unlikely that this association was fortuitous, for these patients were from a total of eight referred for investigation of hirsutism, and pelvic tuberculosis is now a relatively rare disease.

In these patients hirsutism developed remarkably rapidly, and definite virilism was present within six months. In one patient the onset was associated with exposure to open tuberculosis some 4 to 9 months previously. Her hirsutism regressed significantly with antituberculous treatment. In another patient hirsutism developed during the 12 months following an endometrial biopsy which showed active tuberculous foci. None of the patients had a family history of hirsutism. The evidence, therefore, favours the view that the pelvic infection caused the hirsutism.

In each patient there was some evidence which pointed to the adrenals as the direct cause. The 17-ketosteroid excretion was slightly elevated in all cases; in two excretion was significantly depressed after administration of cortisone. In one patient virilism was apparently completely cured by left adrenalectomy; in this case no antituberculous drugs were given.

It is probable that in the past we have been missing this association. Certainly any patient who presents with hirsutism of recent origin, with a normal or slightly elevated 17-ketosteroid excretion, with any symptoms suggestive of infection (such as loss of weight and loss of energy with raised erythrocyte-sedimentation rate), and with a positive tuberculin test, should be considered as a potential case of pelvic tuberculosis.

A search of the literature has revealed no previous reference to such an association. It may well be that in previous decades most women contracted primary tuberculosis at or before puberty. In our patients the hirsutism was more severe as the age of onset increased. A population in which the onset of primary infection is delayed to an older age-group may be the only source of such a clinical manifestation.

The condition referred to here does not appear to be identical with the Stein-Leventhal syndrome, in which wedge-resection of the ovaries is reported to improve the symptoms. None of our patients had the characteristic bilateral ovarian enlargement with luteinisation of theca cells, though in one there were multiple small cysts. The evidence of adrenal origin is also in contrast to the commonly defined picture of Stein-Leventhal syndrome.

1. Powell, D. E. B., *J. clin. Path* 1957, **10**, 262.
2. Toohey, M., *Brit. med. J.* 1950, i, 518; *Ibid*, 1953, i, 650.
3. Biggs, R., Macfarlane, R. G., *J. clin. Path.* (1949), **2**, 33.

The pelvic lesion is not necessarily tuberculous. Any condition which causes a "frozen pelvis" could possibly cause the same syndrome of hyperadrenalcorticism. Dr. C. Coyle, Master of the National Maternity Hospital, Dublin, saw such a patient some months ago. At laparotomy by Dr. D. M. Thomson, of Ottawa, she was found to have pelvic endometriosis.

University College, and
St. Vincent's Hospital, Dublin. D. K. O'DONOVAN.

SUXAMETHONIUM PARALYSIS REVERSED BY EDROPHONIUM

SIR,—Students of muscle relaxants will be interested to hear of a case of "dual block" in an apparently healthy woman of 38 following suxamethonium (50 mg.), which was reversed by edrophonium. Such a reaction has been anticipated but not reported. Full details will be published later.

The sequence was papaveretum (gr. $^1/_3$) and scopolamine (gr. $^1/_{150}$) at −160 minutes; thiopentone 0·5 g., suxamethonium 50 mg., endotracheal nitrous-oxide, oxygen, trichlorethylene. Paralysis was still complete 30 min. later, there having been no response to nalorphine 10 mg., methedrine 15 mg., nikethamide 4 ml., tracheal stimulation, and 10% carbon dioxide. Complete reversal followed 60 sec. after edrophonium 10 mg. ('Tensilon'), and was maintained for 10 min., but relapse followed 20 min. later. Respiration remained inadequate for 5½ hours, during which time neostigmine 2·5 mg. was given and ventilation was maintained with a Beaver respirator. At 7½ hours breathing was again shallow and responded again to edrophonium. There was no further difficulty.

The patient was conscious most of the time. Her plasma-cholinesterase and electrolytes were normal. A neurologist subsequently diagnosed probable disseminated sclerosis with a lesion in the dorsal region.

It seems that, in a properly managed anæsthetic, if paralysis from suxamethonium lasts more than 20-30 minutes, it would be advisable to use edrophonium as a diagnostic test for a dual block rather than give other stimulants; and, if reversal takes place, to follow immediately with atropine and neostigmine to prevent recurrence of paralysis. The patient should then be kept under observation for 8 hours or longer, with means of artificial respiration to hand.

Chislehurst,
Kent. JOHN BULLOUGH.

THE CIRCULATION OF THE NERVE IMPULSE

SIR,—The historian of neurology takes great interest in Dr. Gooddy's new and original design of the nerve impulse (Sept. 7). The idea of a circulation immediately calls to mind that of a fluid. The earliest interpreters of the nerve impulse believed in its "etherial" nature. With Borelli's (1608–1679) postulate of a *succus nervosus* we witness the passage so significant of modern medicine of a metaphysical concept of the nerve impulse to a physical one. It seems that Louis Rolando (1773–1831) was the first to compare the hypothetical nervous power or the equally hypothetical nervous fluid with the galvanic fluid. In the nineteenth century the hypothesis of the nervous fluid suffered its fatal blow from two rising sciences—neuroanatomy and neurophysiology.

Dr. Gooddy's interesting suggestion to conceive the nerve impulse as a circulating agent ultimately rests on reasoning by analogy which, repeatedly, proved in the past to have a great impact on medical thought, ever since the days of the Greeks. The idea of the circle as the ancient symbol of life obviously assisted Dr. Gooddy in conceiving his design, just as it did assist Harvey in conceiving the idea of the circulation of the blood before Harvey actually tried to demonstrate it by observation and experimentation.

I understand Dr. Gooddy's design to be a purely physiological one involving motion and sensation as the sole principles of animal life and nervous activity. Therefore, I can see no threat to the design from "original thought" or "free will" (should this be granted). Nor do I believe that the idea of the circle implies an endless repetition of the same phenomena. I would rather believe that physiological processes, circulating or not, are at the service of metaphysical data, such as original thought or free will, but that they are not synonymous with them. The nervous system, inclusive of the nerve impulse and all of its other equipments, is an organ; the great thinkers of the past, Aristotle, Galen, Descartes, Kant, conceived the organs of a living body as instrumental in thought, but not on equal rank with it. The one cannot be expressed in terms of the other; thought can not be said to line itself up integrally with neurophysiology.

Medical College of Virginia,
Richmond, Virginia. WALTHER RIESE.

ANABOLIC EFFECTS OF ATARACTICS

SIR,—"Animal protein factor" was a presumed essential constituent of diets for non-ruminants, absent from materials derived solely from plants. When vitamin B_{12} was isolated from liver, its identity with A.P.F. was assumed, and when antibiotic manufacturers found that their liquors contained B_{12} they introduced the dried product into animal husbandry under the title A.P.F. We, and others, have been using these A.P.F.s in human nutrition for many years. They tend to reverse the catabolic trend in some patients with cachectic diseases. Crystalline cationic types of streptomyces-derived antibiotics, as well as androgenic steroids, certain arsenicals and antimonials, and isoniazid, were sometimes found to have this effect. Vitamin B_{12} did not seem to contribute to this activity so A.P.F. in its original connotation was dropped. But from habit and for convenience we transferred the name to "anabolism-promoting factor(s)."[1]

In an effort to decide how A.P.F. worked, the following purely descriptive properties of this protean group were defined [2]:

1. They enhance protein utilisation in domesticated omnivores (which, of course, includes man), permitting growth or tissue restitution with a lower level of protein intake than would be the case without them. Cachectic patients put on weight and the increase in appetite sometimes amounts to bulimia.

2. They reverse the toxicity of the folic-acid antagonist, aminopterin, in weanling rats. Whether this is due to permissive folic-acid synthesis in the intestinal tract, or to some other mechanism is unknown.

3. They change the intestinal flora to a predominantly saccharolytic mode, and intestinal bacterial proteolysis is curtailed. Indican excretion drops during their administration. This reversion is partly responsible for the enhanced growth-rate in poultry and hogs given A.P.F., but the exact mechanism is still debated. Certainly, if bacterial degradation of essential aminoacids from food protein is curtailed, some of this ingestate otherwise deflected for the nutriment of proteolytic bacteria would accrue to the host. An alternative theory is that there may be increased formation by saccharolytic bacteria of essential carbohydrate fractions for "ground-substance" synthesis by the host.[3] In any event, malodorous lesions or subjects lose this odour when A.P.F. is administered. Such odour usually derives its "body," though not necessarily its essence, from enterogenous indole and skatole. A simple empirical guide for the quantity of streptomyces antibiotic to be used in the original A.P.F. schedule was the maintenance of an odourless, bulky, soft stool [4] and we eschewed opiates and barbiturates mainly because they made this impossible. Anti-histamines did not affect the stool and we used them routinely as tranquillisers in patients with neoplasm and serious collagen-vascular disease who were being treated with the anabolic modalities.[5]

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3. Barnard, R. D., *N.Y. St. J. Med.* 1957, **57**, 3026.
4. Barnard, R. D. *Ibid*, 1950, **50**, 1852.
5. Barnard, R. D. *Ibid*, 1953, **53**, 93.

With the wider use of so-called ataractics for patients in this and other categories, phenomena reminiscent of this A.P.F. effect began to emerge:

1. Rauwolfia extracts and the promazines are in current use to improve nutrition in hospital patients, some of whom have shown a bulimic response.[6] This, like the remarkable benefit derived from meprobamate in some patients with neoplasms,[7] and comparable findings with promazine in such patients,[8] seems to be more than the improvement in "emotional climate" to which it is ascribed.

2. Reversal of aminopterin toxicity in weanling rats by meprobamate has been reported.[9]

3. Two years ago we reported that a saccharolytic reversion took place in the faecal flora of patients receiving meprobamate. The results of in-vitro bacteriological study were inconclusive. There was some diminution of indole production in mixed faecal cultures containing meprobamate. We have had a number of patients with neoplasms in whom an odourless, bulky, soft stool, initiated by antibiotic administration, has been subsequently maintained for months on meprobamate alone. Dr. V. M. Pennington, in a report to the American Psychosomatic Society, has confirmed our coincident finding of a diminution of body malodour in some such patients.

When ataractics are given to animals as feed-supplements, they appear to produce the same anabolic effect as antibiotic addition.[10] A popular explanation of this finding is that they relieve the animal of "stress" and permit it to develop an unfrustrated eating-pattern.[11] Whether this would be equivalent to good table-manners is not stated, but the explanation is reasonable since the human is not the only domesticated animal with neuroses, or likely to have them manifest gustatorily. But reasonable or otherwise, it is not the only possible explanation, and another could be that the ataractics have concomitant anabolic effects.

Laurelton, Long Island, New York.

JAMES F. BARNARD
ROBERT D. BARNARD.

CORTISONE AND HYPOGLYCÆMIC SHOCK

SIR,—There is ample evidence that cortisone can raise resistance to certain forms of shock, and we have tried its effect on shock due to hypoglycæmia.

In nine male rabbits, weighing about 3 kg. each, hypoglycæmic shock was brought about by 20–40 units of insulin intravenously. The seizures were controlled by glucose. Subsequently the animals were treated for 8 days with 7·5 mg. cortisone acetate twice daily. On the 5th day of treatment, the test was repeated using the dose of insulin which had previously caused shock. On the 8th day of treatment, insulin was given to six animals and, to increase its effect, 1·5% $NaHCO_3$ was given intravenously. 8 days after stopping cortisone treatment, the test with insulin and $NaHCO_3$ was repeated in the same animals. Blood-sugar levels were determined in each case before insulin and then every 30 minutes for 4 hours.

During cortisone treatment hypoglycæmic shock could not be induced in any of the animals. After treatment had been stopped, the hypoglycæmic attack developed again in every case.

The cortisone treatment significantly increased the fall in blood-sugar, due to insulin, in eight animals out of nine—on the average from 59·5 mg. to 115 mg. In six cases, not only was the fall increased, but blood-sugars fell to a lower level than before cortisone treatment.

The effect of cortisone in decreasing susceptibility to seizures was proved in another series of experiments.

In six male rabbits weighing about 3 kg., seizures were brought about with 0·5–0·8 ml. leptazol intravenously. After 8 days of cortisone treatment, two or three times more leptazol was needed to induce seizure. Thus, cortisone treatment seems capable of decreasing the susceptibility to leptazol.

Thus, cortisone prevents insulin-induced hypoglycæmic shock (though the blood-sugar fall increases) and it greatly decreases susceptibility to leptazol. This action might be connected with the effect of cortisone on potassium metabolism, since, after insulin shock, prednisone was less potent than cortisone acetate.

1st Department of Pædiatrics, Budapest University Medical School.

L. BARTA
G. SIMON.

PHYSICAL AND MENTAL HANDICAPS FOLLOWING A DISTURBED PREGNANCY

SIR,—Dr. Stott's most interesting paper (May 18) seems to me to permit further statistical estimations. The correlation of the different types of disturbances during pregnancy with the occurrence of malformations given in table VI of his article permits a grouping into disturbances associated with high incidence of malformations and disturbances with lower incidence of malformations, as shown in the accompanying table.

Group	Type of disturbance	Total incidence (N)	No. followed by early illness (E)	No. of malformations (M)	ΦE	ΦM
I	Serious illness, injury, or death of husband or child, + shock, accident (including severe bomb scares)	21	14	8	54·7	38·1
II	Anxiety state + all other types of harassment and distress listed*	35	29	3	65·9	17·0
III	Maternal illness	24	20	4	65·6	24·1

* With exception of "problem family" and "let-down women" resulting neither in early illness nor in malformation (4 cases).

These rough results are transformed into the inverse sine function,[1 2] Φ thus representing the proportion of Es and Ms on a scale ranging from 0 to 90 angular degrees. The differences of Φs are suited to a provisional "studentisation" by entering the t-distribution[1] with $(N_1+N_2)/2$ degrees of freedom.[3 4] This allows a statistical estimation of differences not principally restricted by too small numbers, as is the case with the chi-square method.

The resulting t-values are:

Difference Φ_M, group I–II = 2·66; n = 28; P < 0·02, > 0·01.
Difference Φ_M, group I–III = 1·65; n = 22; P > 0·05.

Moreover, the exact probability in such cases can be calculated by direct combinatorial analysis.[5] Thus, P for the difference M, group I–II, is found to be 0·0102, which is in fair accord with the results obtained by the much less laborious inverse-sine transformation method.

These statistical results may be regarded as evidence that certain types of psychological damage in pregnancy are more "dangerous," as far as malformations are concerned, than other types. It seems that traumata associated with "near-death" experiences resulting in emotions of long duration are associated with a high incidence of malformations. This might be a useful guide in the further exploration of the interesting psychosomatic correlation shown by Dr. Stott to exist between psychological disturbances of pregnancy and handicaps of the newborn.

Universitäts-Strahleninstitut, Berlin-Charlottenburg, 9.

P. KÜHNE.

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CARCINOMA OF THE PENIS IN TWO BROTHERS

SIR,—We have observed carcinoma of the penis in two brothers. Since this is a rare site for carcinoma, the occurrence of the disease in two members of the same family raises the possibility of hereditary factors. We could find no other reported instance of familial incidence of this disease.

CASE 1.—A farmer, aged 53, had at birth a rather long prepuce which could not be drawn back. Below it smegma accumulated and the mucous membrane was often infected. In 1951 the inflammation became more persistent, accompanied by itching. Copious seropurulent secretion flowed from under the prepuce. Some months later he had pain when urinating. The jet of urine became more tenuous and weak. Knotty, solid growths were felt under the prepuce, and partial circumcision was performed. An inflamed and ulcerated new growth of the penis was disclosed. After the operation he was given deep X-ray therapy. The tumour regressed, but the ulceration remained indolent and urinary complaints increased. At the end of 1952 he was seen at this Institute.

The neoplasm by now involved not only the glans but also the sulcus coronarius and the corpora cavernosa. The glans was mostly destroyed. He was treated by application of radium (10,000 γr); the infiltrations shrank and all lesions cicatrised. A month after healing was complete, the inguinal lymph-nodes were extirpated, and no evidence of metastasis was found therein. He was normal otherwise.

Towards the end of 1955, after an injury with infection, severe necrosis of the penis necessitated a radical amputation. After discharge, the scrotum and lower limbs became swollen. He was admitted for the third time, with recurrent carcinoma of the skin of the scrotum, but no evidence of regional or distant metastasis. Orchidectomy was performed in March, 1955. A year later he died of gangrene of the left leg.

Microscopic study revealed the typical picture of prickle-cell carcinoma, with, here and there, features of keratinisation. There was a striking tendency to deep infiltration.

CASE 2.—The brother, also a farmer, aged 60, had also had a long prepuce since birth. He had often had inflammation of the mucous membrane of the glans and erosions on the inner surface of the prepuce. In 1956, during such a bout of inflammation, he was given X-ray therapy (600r in 8 sittings every other day). A month or so before he was admitted, a small erosion appeared close to the external opening of the urethra.

On examination here, the inner surface of the prepuce was mother-of-pearl in colour, smooth, and atrophic. The mucous membrane of the glans was largely pink but not shiny. On the back of the glans was a raised plaque, close to the external urinary meatus, as large as a finger-nail, showing a sallow colour and a rough surface. No swollen lymph-nodes could be felt in the groins.

Microscopy showed a well-differentiated prickle-cell carcinoma, with papillomatous structure and a pronounced stromal reaction. The intact epithelial covering of the glans showed signs of acanthosis.

Circumcision and postoperative radiation therapy were suggested, but he refused.

These two cases raise the question of how far such a simultaneous carcinomatous new growth at the same site in two brothers may be attributed to factors running in the family. But reliable statistical and epidemiological investigations [1 2] show that at this site there is no reason to invoke heredity (as in multiple polyposis of the alimentary tract or retinoblastoma). Carcinoma of the penis has some racial as well as geographical differences, which may be explained by other, non-genetic factors, above all by ritual customs.[3–5] The association of the two cases seems therefore to be fortuitous.

Both men had a long prepuce and phimosis, which, with poor personal hygiene, led to accumulation of smegma and chronic inflammation, which might cause precancerous changes of the epithelium. In case 2 there was an acanthosis (i.e., a manifestation of intra-epidermal carcinoma). Moreover, the second patient underwent X-ray therapy of the glans and prepuce, which might have a carcinogenic influence.

V. MIKHAILOV
R. RAITCHEV
V. ANDREEV.

Institute for Oncological Researches, Sofia, Bulgaria.

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METALLIC CORROSION IN ORTHOPÆDIC SURGERY

SIR,—In suggesting that metal fillings in teeth might play a part in the electrolytic degeneration of metallic implants, Mr. Hovell (Oct. 5) exhibits a fallacious line of reasoning that is very common.

The fact is that dissimilar metals have no effect upon each other unless they are in electrical contact with each other (in addition to being bathed in the electrolyte). By analogy with a flash-lamp battery, no current flows and no chemical action takes place unless and until the positive and negative poles are connected by a wire. Thus while a screw of one metal in metallic contact with a plate of another will affect each other electrolytically, two screws of dissimilar metals in different parts of the body (or, probably, even in the same bone so long as they are not in metallic contact) do not. Similarly a metal filling in a tooth will not affect an implant in a distant part of the body.

The mistake originates from Venable and Stuck's work which has been responsible for considerable over-emphasis (except in France) upon the electrical effects, and neglect of the toxic effects, of metals upon tissues.

Birmingham Accident Hospital. J. H. HICKS.

CORTISONE THERAPY IN EARLY PREGNANCY: RELATION TO CLEFT PALATE

SIR,—Harris and Ross [1] describe a baby with a cleft palate whose mother had been given cortisone in early pregnancy. Lardelli and myself [2] reported the case of a woman with pituitary basophilism who gave birth to a child with cleft palate. This complements the experience of Fainstat [3] on the action of cortisone in rabbits and rats, and the dangers of the prescription of corticosteroids in early pregnancy.

J. DE LA HIGUERA ROJAS
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EFFECT OF VITAMIN B_{12} ON ANOREXIA

SIR,—Vitamin B_{12} (cyanocobalamin) has been shown to play a significant part, not only in erythropoiesis, but also very widely throughout Nature in enzyme reactions concerned in intermediate cell-metabolism. This has led to the view that mild deficiency of vitamin B_{12}, insufficient to produce macrocytosis, may lead to various disturbances including anorexia.[4]

In order to determine whether vitamin B_{12} has any "non-specific" effect on anorexia (i.e., in patients who show no evidence of vitamin-B_{12} deficiency), I have carried out an experiment—statistically planned and controlled throughout—on a series of patients in whom anorexia was a prominent and troublesome feature. The experiment comprised two concurrent trials, one using the method of sequential analysis [5] and the other a formal "double-blind, switch-over" using each patient as his own "control."

The "control" preparation was a pleasantly flavoured syrup containing 7 mg. of ascorbic acid per 10 ml. dose (one teaspoonful = 1 fluid drachm), and the "active" preparation was similar in all respects except that it also contained 20 μg. of vitamin B_{12} per 10 ml. dose. 1 teaspoonful was given three times a day before food.

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The series comprised 7 patients, whose ages ranged from 61 to 80 years (average 69) and in whom the diagnoses were: chronic lung abscess, pan-hypopituitarism, chronic congestive heart-failure due to ischæmic heart-disease (2 cases), carcinoma of the uterine cervix, cerebral thrombosis with hemiplegia, and convalescence following pneumonia. The anorexia in all cases was sufficiently severe to be an obstacle to the smooth management of the case.

The results showed no difference between the "active" and the "dummy" preparations, and "sequential analysis" indicated that no further useful purpose would be served by continuing the experiment beyond the 7th patient.

It is therefore firmly concluded that vitamin B_{12} has no effect on anorexia in elderly people. (It must be emphasised that this investigation is not concerned with the anorexia sometimes associated with pernicious anæmia and other overt B_{12}-deficiency diseases.)

The preparations used in this trial ('Ce-Cobalin' syrup and the "control") were supplied by Messrs. Paines & Byrne, of Greenford, Middlesex.

The Cowley Road Hospital, Oxford. P. D. BEDFORD.

*MEPROBAMATE

SIR,—In the children's ward of the Rigshospital, where about 600 children with cerebral pareses are treated, various drugs affecting the cerebrum, the extrapyramidal system, or the muscles have been used during the past few years without appreciable benefit.

In the past two years encouraging reports have come from the United States of meprobamate, and during the past six months we have been evaluating this compound in patients with cerebral pareses.

Berger [1] has shown that the drug acts on the central nervous system, and in particular blocks the interneuronal synapses in the thalamus. It does not significantly affect the autonomic nervous system. Its toxicity is low, and in experiments in animals it has had a quarter the toxicity of the barbiturates.[2,3] Clinically it has been shown to be of value in anxiety and tension states. Gillette,[4] who gave meprobamate to 28 patients with cerebral palsy, obtained a good response in 75%.

We have studied 33 patients with cerebral palsy. 31 of these were children aged 2–10 years; and 2 were adults under 27. The children under 5 were given 100 mg. two to four times daily, and older children had 200 mg.

Throughout the trial there were no abnormal chemical findings in blood and urine, and few side-effects. Several children grew very sleepy and unmanageable when the dose was increased, but this symptom disappeared quickly on decreasing the dose or discontinuing the meprobamate.

Diagnosis	No. of patients		
	Improved	Not improved	Total
Athetosis	0	7	7
Tetraplegia	12	4	16
Paraplegia	2	1	3
Hemiplegia	3	4	7
Total	17	16	33

17 of the 33 patients improved during treatment. There was no benefit in the athetotics, though Gillette stated that they were exceptionally responsive to meprobamate. In the 17 patients who responded well the effect was predominantly tranquillising in 11: they became bolder in walking and less agitated; in 4 the speech was better, in 3 eating was improved, and in 15 muscle exercises were easier. In 14 patients the spasticity of the muscles was reduced. The results are set out in the accompanying table.

No trials with placebos were carried out.

We had previously noted that primidone ('Mysoline') had an obvious tranquillising effect in patients with athetotic hyperkinæsthesia. The voluntary movements became easier and more controlled. The daily dosage was 25–250 mg. Meprobamate was, therefore, administered at the same time as primidone. A better effect was noted than when the two drugs were given separately. These results are encouraging and further trials should be made of meprobamate in cerebral pareses.

'Miltown' was kindly made available by Lederle Laboratories.

Rigshospital, Copenhagen. K. H. SPARUP.

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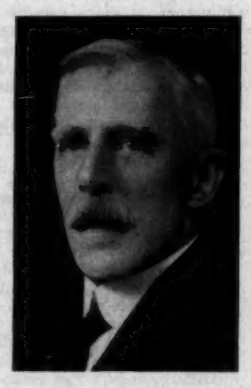
Obituary

JOHN HERBERT PARSONS

Kt., C.B.E., M.B., D.Sc. Lond., LL.D., F.R.C.S., F.R.S.

Sir John Parsons, who died on Oct. 7 at the age of 89, was recognised by his colleagues and patients as an outstanding and sympathetic clinician. By the physicists, physiologists, and engineers to whose work on vision and lighting he offered the assistance of ophthalmology, he was also recognised as an outstanding scientist. By his work and his character he had won the admiration and affection of both groups.



He was born in Bristol, and he began his scientific education in the university there, where he held a Gilchrist scholarship. He continued his studies in London at University College and took the B.SC. Lond. with honours in physiology in 1890. Two years later he took the M.B. from Barts. For a time he acted as assistant to Schäfer at University College. His interest in physiology remained with him all his life, but he now turned especially to ocular physiology. About this time he began his association with the Royal London Ophthalmic Hospital, at first as a clinical assistant and later as curator and librarian; and the background of the four volumes of his *Pathology of the Eye*, the first of which appeared in 1903, was the museum at Moorfields. This immense work not only won lasting fame for its author but changed ophthalmology from an empirical to a scientific specialty, and attracted students to Moorfields from all over the world. In 1903 Parsons was appointed to an Arris and Gale lectureship of the Royal College of Surgeons of England, and he received the Middlemore prize in 1904. The same year he became assistant ophthalmic surgeon to University College Hospital. The staff of this medical school at that time has been described as "a collection of isolated geniuses"; Parsons in his own way maintained the tradition of genius if not of isolation. In 1907 appeared his *Diseases of the Eye*, a beautifully written, compact, yet comprehensive book, which under Sir Stewart Duke-Elder's editorship is still known to every ophthalmologist.

But even in these early busy years of writing, teaching, and practising, Parsons found time to study the practical conditions of lighting and how they might affect the hygiene of the eyes. In 1909 he helped to found the Illuminating Engineering Society, which was set up to "investigate lighting scientifically and to disseminate knowledge which might lead to improved standards of practice." Parsons became the first chairman of the council of the society, having with characteristic modesty declined the presidency because he thought the first president should be a physicist or an engineer. He read the first technical paper to the society, taking as his

subject Glare, its causes and effects. In 1921 he served a term as its president, and he was elected an honorary member in 1943.

As a member of the Home Office Departmental Committee on Lighting in Factories and Workshops, set up in 1913, Parsons visited many factories and acquired a first-hand knowledge of industrial conditions. After the Factories Act of 1937 made "sufficient and suitable lighting" in all factories obligatory, the committee was reappointed to advise the Minister as to the standards to be prescribed. Parsons was again a member, and in 1940 he signed its fifth and last report, on which the present Factory Lighting Regulations are based.

From 1928 to 1932 he was a member of the Medical Research Council, and he was chairman of the council's physiology of vision committee. He was also a member of the illumination research committee of the Department of Scientific and Industrial Research. His enthusiasm for research made him most anxious for the establishment of an institute of ophthalmology in London. Between the wars he was in touch with the Rockefeller Foundation, and he had great hopes of obtaining a grant from that body. However, first the financial recession in the 'thirties and later the war postponed these hopes, and when the institute of ophthalmology of London University was finally established he was immensely gratified.

The impressive lists of reports published by the committees on which he sat are tangible evidence of his influence. Less tangible but perhaps even more important was the encouragement he offered to young workers. Of these K. T. writes:

Sir John's vast knowledge and scholarly approach to the subject provided the best possible example for anyone beginning work on vision; and his unfailing interest and help, not only in the form of encouragement but of practical assistance, made a great difference to us all when we were comparatively unknown and very junior. I remember several delightful tea parties at his house in Queen Anne Street before the war, made memorable by most helpful discussions in which his whole tremendous knowledge was at one's disposal. Even after the war, long after he had retired, Sir John was present and often played the host at gatherings of those interested in the scientific aspects of vision. I particularly remember him at the Thomas Young oration given in 1945 by Prof. Ragnar Granit. At that time Granit's electrophysiological work on the colour mechanisms of the retina was unfamiliar and his results were hard to understand in relation to the then accepted theory. Sir John was frankly sceptical of their importance. But his mind was elastic enough to embrace new ideas and eight years later (in the introduction to the *British Medical Bulletin* on the physiology of vision) he wrote that Granit's work on the neurophysiology of vision had been "epoch-making" and his discovery of dominator and modulator curves "of great significance."

Of his philosophical writings his colleagues knew less, but as H. C. W. writes:

Some inkling there was in 1918 when Parsons published *Mind and the Nation*, and again when he was 82 and published his last book, entitled *The Springs of Conduct*. Naturally it was on informal occasions that one came to know best the inner man behind the façade with which, like most of us, he faced the world. He was not demonstrative but he made abiding attachments. Of course he was critical—no-one with such a penetrating and analytical mind could be otherwise—but he did not stint praise when praise was due. His affection for those who captured his interest, either by their personalities or the merit of their work in those fields of study dearest to his heart, was sincere, and he inspired in them not only the feeling of respect due to a man of his erudition but also a feeling of almost filial affection.

During the 1914–18 war Parsons had served as consultant ophthalmologist to the Armed Forces with the rank of colonel A.M.S., and after the war he served on the advisory medical councils of the Air Ministry and the Admiralty. For these official services he received his first official honours. He was appointed C.B.E. in 1919 and knighted in 1922. His academic honours included his election as F.R.S., and honorary degrees from the Universities of Edinburgh and Bristol. When he visited the United States in 1936, while holding the presidency of the Royal Society of Medicine, he received the Lucien Howe medal of the American Ophthalmological Society.

In 1948 the Faculty of Ophthalmology and the Ophthalmological Society of the United Kingdom presented him with his portrait as a gift from his English colleagues to mark his 80th birthday. Two of them have sent these tributes to their friend. H. N. writes:

Parsons' manner was a little reserved, but this was the remnant of shyness from which he confessed that as a young man he had suffered. This doubtless also accounted for his quiet manner of speaking in public, as when reading a paper at a professional meeting or when making a speech. His wide knowledge of the English language and his mental agility made it sometimes not too easy for those less well equipped to follow him. One of his greatest affections was for music, and in earlier years he used to attend orchestral concerts and follow the music in a miniature full score. As a colleague he was admirable, always ready to interest himself and to help in any professional problem.

R. A. G., who was one of Parsons' students at Moorfields, returns to his work as a teacher.

Before the first war, numerous students from America who then thronged the hospital and who knew of his international reputation, crowded round him. He was, however, inclined in the course of his teaching to forsake purely clinical matters and to discuss somewhat abstruse problems concerning the physiology of vision and the higher mathematics of optics, which were above the level of education of the average student. When Parsons reached the recognised retiring age of 60 from the staff of Moorfields, the committee of management waived their usual rule so that he continued to serve on the active staff till he reached the age of 65, and, as far as I know, his is the only case in which this rule was set aside.

Parsons was an omnivorous reader and his interest in and knowledge of many subjects were unrivalled. These, in addition to more mundane subjects, included pathology, physiology, psychology, mathematics, and to some extent music; of this last, perhaps, his appreciation was chiefly intellectual. He was an inveterate traveller, and besides his visits to the U.S.A., where he had numerous friends and admirers, he managed to see a good many European and other countries. Even late in life he undertook yearly cruises.

He did not suffer fools gladly, and at times was inclined to be somewhat hasty in his judgment of people. This trait combined with a satirical sense of humour no doubt occasionally gave offence, but even his most caustic sallies were ever accompanied by a kindly and disarming twinkle of the eyes, and he would always listen, however disapprovingly, to the other man's point of view. He dearly loved an argument. His mind and memory remained unclouded till the end and his conversation always stimulating, but of later years his increasing deafness made verbal interchange of ideas more difficult. Parsons as a friend was a most lovable and human person, possessed of one of the most brilliant intellects with which it has been my good fortune to be associated. He was truly a very great man.

Appointments

DE SWIET, JOHN, M.D. Lond., M.R.C.P.: additional consultant in general medicine, Pontypridd and Rhondda H.M.C. area.

FRANCIS, H. W. S., M.B. Cantab., D.P.H.: assistant administrative M.O.H., Birmingham.

HUNTER, A. N., M.B. Glasg., D.P.H.: senior assistant M.O. (headquarters staff), Norfolk.

KENNEY, Patricia M., M.B. Lond., D.C.H.: assistant M.O., Surrey.

MCCALLUM, J. R., M.B. Edin., F.R.C.S.E.: consultant E.N.T. surgeon, Edinburgh northern group of hospitals and Royal Hospital for Sick Children, Edinburgh.

OLIVER, R. M., M.B. Lond., M.R.C.P., D.C.H.: assistant M.O., Surrey.

O'ROURKE, Florence L., M.B., N.U.I., D.P.H.: school M.O. and assistant M.O.H., Derby.

PURCELL, W. M. O., M.D., N.U.I., M.R.C.P., D.M.R.D.: assistant in the department of X-ray diagnosis, Middlesex Hospital, London.

Liverpool Regional Hospital Board:

EDINGTON, G. M., M.D. Glasg., D.C.P., D.T.M. & H.: consultant pathologist, Whiston and Rainhill Hospitals.

HENNESSY, D. P., M.B., N.U.I., D.P.M.: consultant psychiatrist and deputy medical superintendent, Winwick Hospital.

KEIDAN, S. E., M.B. Lpool, M.R.C.P., D.C.H.: consultant paediatrician, Royal Liverpool Children's Hospital and Broadgreen Hospital.

LITTLER, T. R., M.D. Lpool, M.R.C.P.: consultant physician, Birkenhead General Hospital.

MARTLEW, R. H., M.D. Lpool, D.P.M.: consultant psychiatrist and deputy medical superintendent, Rainhill Hospital.

ROWLANDS, IRENE P., M.R.C.P., D.P.M.: consultant physician in geriatrics, Chester and Warrington areas.

Notes and News

THE ROYAL EYE HOSPITAL

A THANKSGIVING service in Southwark Cathedral on Oct. 22 at 3.30 p.m., when the Bishop of London will preach, will commemorate the centenary of this famous hospital. It was opened by John Zachariah Laurence on Oct. 12, 1857, at 6, St. George's Circus and named the South London Ophthalmic Hospital. For the first three years of its life Henry Maudsley was treasurer and chairman and its early surgeons included Robert Brudenell Carter (1870–77), who succeeded Laurence, and Malcolm Macdonald McHardy (1877–1909). At the time of its inception there were already 12 ophthalmic institutions in London and 25 in the provinces, but this was the first in South London, then rapidly becoming industrialised. Like almost all special hospitals its foundation was opposed by the profession as a whole and like all charitable institutions of this time the original makeshift premises soon proved inadequate.

In 1892, after eighteen frustrating years of abortive negotiation and much planning, a new hospital with 40 beds was opened on the present site at a cost of £34,000. It is significant that the first estimate to build and equip the new hospital drawn up in 1880 on the basis of 30 beds was but £8000. Prof. Arnold Sorsby, in his interesting history [1] of the hospital, attributes the enormous difference between estimate and eventual cost to "greater ambitions" necessitated by the growing demands on the hospital.

When the new hospital was opened it was right up to date with fireproof doors, staircases designed especially for the blind, lighting by electricity, and a refreshment bar. But once again the demands of the public exceeded the supply of amenities, and by 1902 the overcrowding was becoming serious. Festival dinners and other expedients were invoked to eke out income, and step by step the beds were with ingenuity increased to 55. The site of the old Surrey Theatre was purchased in 1931 and its demolition completed four years later, but rebuilding receded as war became more certain. In 1941 the hospital was seriously damaged by incendiary bombs, and 85 beds were made available in Surbiton for the patients, who fortunately had suffered no harm. In 1944, 64 beds were found at Lambeth Hospital. The last twenty-five years have provided, as Professor Sorsby relates, "the same back-breaking work, the same heavy obstacles, the same drawn-out hopes but also the same steady, increasing progress towards a clearly perceived goal."

THE NURSE AS STUDENT

THE technique of job-analysis, which was used in the Nuffield Provincial Hospitals Trust's study of the work of nurses in hospital wards, has now been applied to the work of student nurses. Mr. H. A. Goddard, who was associated with the Nuffield report, has relied on it, as well as on questionnaires and interviews, in the investigation which he has lately made for the South East Metropolitan area nurse-training committee.[2] He considered the work of student nurses in 10 different hospitals, and found that they spend about 87% of their available time in nursing duties and 13% in theoretical training. The amount and range of practical experience that the student gains during her nursing duties apparently varies greatly from hospital to hospital. This probably is because the allocation of a nurse's time, especially when staff of all grades is scarce, must often depend on the patients' needs. This may be inevitable, but equally inevitably, as Mr. Goddard's evidence confirms, it means that her time is not always spent to her best advantage as a student.

INDUSTRIAL MEDICINE ON TYNESIDE

THE Nuffield department of industrial health, King's College, Newcastle upon Tyne, has completed its first decade. Its report [3] for 1951–56 gives some indication of the range of its investigations—from hand injuries to vanadium poisoning (a hazard which may increase) and from coalminers' pneumoconiosis to experimental psychology. Under the direction of Dr. R. C. Browne, the Nuffield professor, the department also engages in advisory work and undergraduate and postgraduate teaching; and a hope is expressed that in future doctors will be taught more about the relationship of work to health, and how "to prescribe work with the same specificity as medicine."

In April of last year a survey was begun of the industrial-health provision in Tyneside; and workers, management, doctors, and nurses are being asked what they think is needed. When all information has been collected, a plan will be outlined for a Tyneside industrial health service. It might take the form of two tiers: (1) a field-treatment tier financed and administered by both sides of industry, and (2) an advisory tier formed by a regional industrial hygiene laboratory. If such a service comes into being, says the report, it will further cement the bonds between the college, local industry, and the National Health Service.

1. Royal Eye Hospital 1857–1957. Pp. 24. 1s. 6d. Obtainable from the hospital, St. George's Circus, S.E.1.
2. *The Work of Student Nurses and Pupil Assistant Nurses.* 1957. P. 56. 2s. (post free from the committee, 11, Portland-place, London, W.1.
3. Nuffield Department of Industrial Health: Second Quinquennial Report. King's College, Newcastle upon Tyne, University of Durham, 1957.

University of London

At recent examinations the following were successful:

D.C.P.—Dulcie Alldis, M. E. Babiker, Monica B. Bishop, Borys Boczarow, P. D. Byers, F. M. Chaudhary, J. S. Cornes, K. G. Gadd, D. J. Hansman, C. O. Le C. Hughes, Charles Isaacson, K. P. Khan, A. S. Khan, P. R. Lim-Chow Lam-Po-Tang, D. C. Mallik, D. P. Manandhar, A. D. Moore, Veluppillai Rajapillai, Harold Rifkin, S. J. Rifkin, C. P. Schwinn, D. A. Sugerman.

D.P.H.—F. L. da Costa, M. M. Hasan, N. V. Karve, W. S. Kulesza, J. E. B. McPhail, M. A. Malik, Phaichitt Siribodhi, Ah Yen Wong Shiu Leung.

University of St. Andrews

Dr. Ronald Davidson has been appointed to an assistantship in pathology in Queen's College, Dundee.

Royal College of Surgeons of England

At a meeting of the council on Oct. 10, with Sir James Paterson Ross, the president, in the chair, Mr. N. R. Barrett was admitted to the court of examiners.

The Mitchiner medal was presented to Lieut.-Colonel P. D. Stewart, the Lady Cade medal to Squadron-Leader E. J. McGuire, and the Handcock prize to A. W. Asscher (London Hospital Medical School).

Diplomas were granted to the following:

F.R.C.S.—G. J. Bendeich.

F.F.A.R.C.S.—Peggy J. Clark-Roberts, T. V. Campkin, Marion E. Record, J. R. E. Jenkins, R. M. Whelan, Shirley F. Dauncey, J. S. Ogilvie, C. D. Sanders, R. G. Milne, C. R. Climie, Pauline W. Balmer, J. D. Bird, W. H. Cochrane, G. W. Burton, D. C. C. Stark, Beatrice M. Evans, D. C. Hodgson, Robert King, Angela Mathie, J. V. I. Young, T. W. Baillie, G. J. Carroll, D. A. Walmsley.

M.R.C.S.—G. Andem, Dorothy L. Hall, J. R. Lang, Jayamanee Venkatasamy, F. C. Worlock.

The following diplomas were granted jointly with the Royal College of Physicians:

D.C.H.—Prem Swarup Agarwal, Ines R. Aldous, D. Y. Al-Faddagh, P. G. Allen, G. L. Asherson, Samira Adib Baban, Dorothy F. Bate, P. C. Bopaiah, Gisela Boss, P. W. S. Broughton, P. G. T. Bye, J. R. L. Carstairs, H. G. Crofts, P. L. de la Harpe, A. H. J. Dobson, W. D. Elliott, P. H. Friedlander, G. F. Gearty, D. D. Gibbs, Janet Goodall, M. J. Harris, Sylvie M. Harrison, Elva G. Haynes, Mary M. Heaf, F. N. C. Ho, Julia C. Hurford, Jack Insley, M. O. P. Iyengar, Lakshmi Janaki, B. R. Jha, D. T. Jones, Kathleen M. Jones, G. E. Kennedy, M. R. Khan, S. R. Khan, P. J. King, Christine Kirby, Siu-Tze Kwan, Fazleabbas Ahmedali Lanewala, G. M. Lewis, Muriel M. Lingwood, K. E. Lovell, Christopher Lydon, John McIntosh, J. B. McWhinnie, P. K. A. McWilliam, Violet Ma Khin Kyi, G. N. Marsh, K. D. Mason, Eve M. Mawdsley, John Meecham, Jagadish Narayan Mishra, Rafiqa Ghulam Mohammad, Joan M. Montague, Violet V. M. Moody, Sayanapuram Nagaswami, C. G. H. Newman, Margaret E. Noad, G. D. Officer, Eileen M. O'Neill, J. W. Platt, D. A. Pottinger, Mary Price, D. S. C. Procter, Masoud Rafaat Hamedani, B. A. J. Reay, C. R. Sexton, Monica Shackleton, Ali Ahmed Shaikh, Margaret H. Smith, B. W. Stein, E. R. H. Tennant, M. K. Thomas, Panchanan Tiwary, Wanda Trowsdale, M. B. Watts, H. J. Weston, Don Somaratna Wijesinghe, Hock Boon Wong, Ethel M. Wright.

D.T.M. & H.—Colundalur Achuthan, Khwaja Muin Ahmad, Tarik Ali Al-Amin, Muhammad Azim Almani, Abdul Ghani Baloch, Ajitkumar Narharishanker Bhatt, Anand Bhoomkar, Syed Lamaat Ahmad Bokhari, R. H. Cox, J. M. Deka, K. C. Durairajah, Hashem Salih El-Dabbagh, Binod Kumar Gupta, Laurence Hall, V. K. Jain, Erasmus Lyngdoh, Om Prakash Mahajan, Olga Mendis, Narendra Mishra, Gottlieb Lobe Money, Protap Kumar Mukherjee, Aswathnarain Nagaraj, J. K. Nayar, Elizabeth S. Ordish, Mrigendra Raj Pandey, Abdul Gaffar Pasha, K. M. Patel, V. R. Patel, Abdul Qadir, M. J. Robertson, Indu Bhusan Roy Chowdhury, Karolina Schonenberger, Mohammad Shareef, Mukteshwar Prasad Singh, G. H. J. Teichler, Margaret H. Tripp, S. A. Wahid, D. E. Worsley.

D.O.—E. R. Asregadoo, Shamrao Manglaji Bele, Gouri Pati Chattopadhyay, Roy Dalgleish, Asutosh Das Sarkar, L. C. Dutta, Zvi Gelman, J. K. G. Grieves, W. D. E. Hamilton, Raymond Harrison, Rosemary Hawe, D. G. Johnston, M. H. Luntz, M. K. Menon, C. A. L. Palmer, J. L. Pearce, G. R. A. Raad, Gopi Nath Saha, M. S. Sampath, U. C. K. Satsangi, H. A. Stein, E. St. E. Thompson, T. N. Ursekar, E. H. Wallace.

D. Phys.Med.—A. W. Burnell, A. L. Bass.

Institute of Dermatology, London

The second semi-permanent exhibition to be held at this institute, Lisle Street, W.C.2, from Nov. 4 to 25, will be by Dr. D. Geraint James and Dr. A. D. Thomson on sarcoidosis.

Institute of Child Health, London

The Simpson Smith surgical essay prize for 1957 has been awarded by this institute to Mr. P. P. Rickham, for his essay on the treatment of ectopia vesicæ and vesico-intestinal fissure.

Central Mediterranean Forces Surgeons Club

The annual dinner of this club will be held on Saturday, Oct. 26, at 7 p.m. at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2. Further particulars may be had from Mr. Harold Burge, 73, Bathgate Road, S.W.19.

British Council for the Welfare of Spastics

At the annual meeting of this council to be held on Wednesday, Nov. 13 at 4.30 p.m. at B.M.A. House, Tavistock Square, London, W.C.1, Prof. Alan Moncrieff will speak on cerebral palsy today. Tickets may be obtained from the secretary, 13, Suffolk Street, London, S.W.1.

West Cumberland Hospital

On Oct. 4 Mr. E. F. Collingwood, chairman of the Newcastle Regional Hospital Board, laid the foundation stone of the West Cumberland Hospital at Homewood, Hensingham, near Whitehaven. The stone was built into the wall of the psychiatric block. The tuberculosis block was opened in January (see *Lancet*, 1957, i, 1051).

Royal Institute of Public Health and Hygiene

This institute has appointed Prof. A. Bradford Hill as the Harben lecturer for 1957. His three lectures will be given at the institute, 28, Portland-place, London, W.1, on Monday, Tuesday, and Wednesday, May 19, 20, and 21, at 5 P.M. His subject will be the experimental approach in preventive medicine.

Nuffield Foundation

In honour of Lord Nuffield's 80th birthday, the Foundation has offered the University of London £80,000 for the endowment of a professorship of child surgery at the Institute of Child Health and the Hospital for Sick Children (Great Ormond Street), and the Fiji Central Medical School at Suva £15,000 to establish a department of social and preventive medicine.

Postgraduate Travelling Fellowships

A limited number of postgraduate travelling fellowships for medical or dental practitioners are being offered by the British Postgraduate Medical Federation to applicants who hold appointments at one of the undergraduate teaching hospitals or medical or dental schools or postgraduate institutes of the University of London. Their aim is to enable those in training as specialists to obtain experience at universities or other centres in the United Kingdom or abroad. Further details will be found in our advertisement columns.

Hospital Building and the National Economy

Mr. Derek Walker-Smith, the new Minister of Health, speaking at the centenary dinner of the Bradford Royal Eye and Ear Hospital on Oct. 7, said that the pace of new hospital building must be linked with the country's economic position. Today good work was often being done in old or obsolescent buildings, and he appreciated that such buildings were not merely tiresome to work in, but often the cause of real harm to the service provided. "We are," he continued, "replacing them as fast as we can. But it would be wrong to give the impression that we can go as fast as we would like in present economic circumstances, and still more wrong to suggest that we can divorce the pace of our progress from the general economic realities of life. We cannot do all we like as fast as we would like. But we are well aware of the needs of hospitals, and we will certainly do what we can in the general context of a sound national economy, on which our hospitals, our social services, and much else besides inescapably and unreservedly depend."

On Oct. 7 Mr. Denis Browne received in Chicago the Ladd medal for pædiatric surgery from Prof. Orvar Swenson, president of the Surgical Section of the American Academy of Pediatrics.

At the Congress of the International Union of Railway Medical Services held in Paris recently, Dr. J. Sharp Grant, regional medical officer, Eastern region, British Railways, who is first vice-president of the union, was presented with the medal and scroll of the City of Paris.

CORRIGENDUM: *Welfare Food Changes.*—Last week (p. 737) we said that manufacturers of proprietary dried milks and infant cereals had been asked to reduce the vitamin-D fortification of their products to 300 I.U. per oz. This is correct only for the cereals.

Diary of the Week

Sunday, 20th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, Gray's Inn Road, W.C.1
10.15 A.M. Mr. Anthony Radcliffe: Common Ear, Nose, and Throat Conditions.

Monday, 21st

HUNTERIAN SOCIETY
8.30 P.M. (Talbot Restaurant, London Wall, E.C.2.) Mr. J. C. Ainsworth-Davis: The Vagaries of Hæmaturia. (Presidential address.)

Tuesday, 22nd

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.C.1
8 P.M. *Medicine.* Dr. W. A. Bourne: Medicine at the Periphery. (Presidential address.)
ST. MARY'S HOSPITAL MEDICAL SCHOOL, London, W.2
5 P.M. Dr. A. M. Joekes: Anuria following Labour and Abortion.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. W. S. Peart: Some Biochemical Aspects of Hypertension.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Mr. K. I. Nissen: Mechanisms of the Carpal Tunnel Syndrome.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. N. R. Mackay: Radiation Physics (first of two lectures).
ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Mr. Rodney Smith: Recent Advances in Pancreatic Surgery.

Wednesday, 23rd

ROYAL SOCIETY OF MEDICINE
5 P.M. *Endocrinology.* Dr. C. N. Armstrong: Clinical Diagnosis of Sex. (Presidential address.)
8.15 P.M. *General Practice.* Dr. John H. Hunt: Peripheral Vascular Disease in General Practice. (Valedictory address.)
POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
2 P.M. Dr. F. V. Flynn: Electrolytes.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Arthur Tickner: Vitamins and Skin Metabolism.
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
5.30 P.M. Dr. Paul Sandifer: Heredo-familial Degenerative Disorders.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Sir Clement Price Thomas: Carcinoma of the Lung.
LONDON COUNTY MEDICAL ASSOCIATION
8.15 P.M. (New End Hospital, N.W.3.) Mr. J. E. Piercy, Dr. Raymond Greene, Dr. A. T. Richardson: Myasthenia Gravis. (A film will be shown.)
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, Portland Place, W.1
3.30 P.M. Mr. W. E. Tucker: The Active Approach to the Treatment of Injuries.
MANCHESTER MEDICAL SOCIETY, Medical School, Manchester University
4.30 P.M. *Pathology.* Prof. N. F. Maclagan: Tests of Thyroid Function.

Thursday, 24th

ROYAL SOCIETY OF MEDICINE
8 P.M. *Urology.* Prof. L. N. Pyrah: The Renal Stone. (Presidential address.)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Prof. G. L. Montgomery: Some Problems in the Pathology of Coronary Artery Disease.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. S. C. Gold: Connective Tissue Diseases.
INSTITUTE OF PSYCHIATRY
3 P.M. (Maudsley Hospital, S.E.5.) Dr. W. H. Thorpe: Drive and Instinct in Animals (second of three lectures).
NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Orthopædic Hospital, Oxford
8.30 P.M. Mr. R. G. Taylor: Studies in American Orthopædics.
HONYMAN GILLESPIE LECTURES
5 P.M. (University New Buildings, Teviot Place, Edinburgh.) Dr. Sheila Sherlock: Complications of Acute Virus Hepatitis.

Friday, 25th

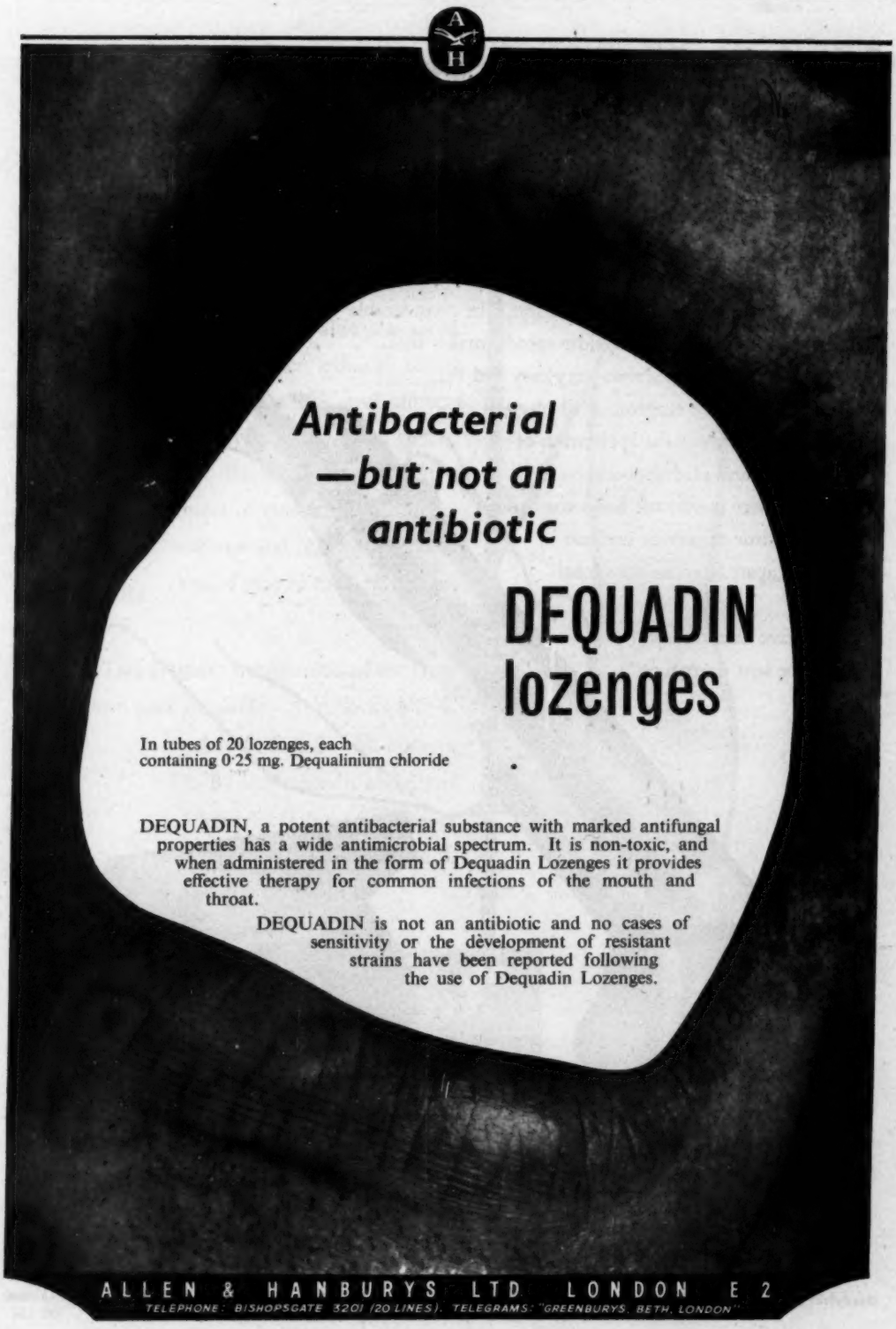
ROYAL SOCIETY OF MEDICINE
5 P.M. *Pædiatrics.* Mr. E. Gwynne-Evans, Prof. C. F. Ballard: The Mouth Breather.
8.15 P.M. *Obstetrics and Gynæcology.* Sir Arthur Gemmell: Some Episodes in Ovarian Surgery. (Presidential address.)
POSTGRADUATE MEDICAL SCHOOL
10 A.M. Mr. W. J. Lytle: The Common Bile Duct.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY
3.30 P.M. Mr. S. E. Birdsall: Injuries to the Nose.
ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH, Edinburgh, 2
5 P.M. Dr. W. Ritchie Russell: The Physiology of Learning. (Morison lecture.)

Births, Marriages, and Deaths

BIRTHS

COOPER.—On Sept. 22, in the Oakville-Trafalgar Memorial Hospital, Ontario, to Elizabeth (née Kirk) wife of Dr. Michael A. Cooper—a son.

HOLLMAN.—On Oct. 10, at University College Hospital, London, to Dr. Catharine Hollman (formerly Large) and Dr. Arthur Hollman—a daughter, Barbara Jean.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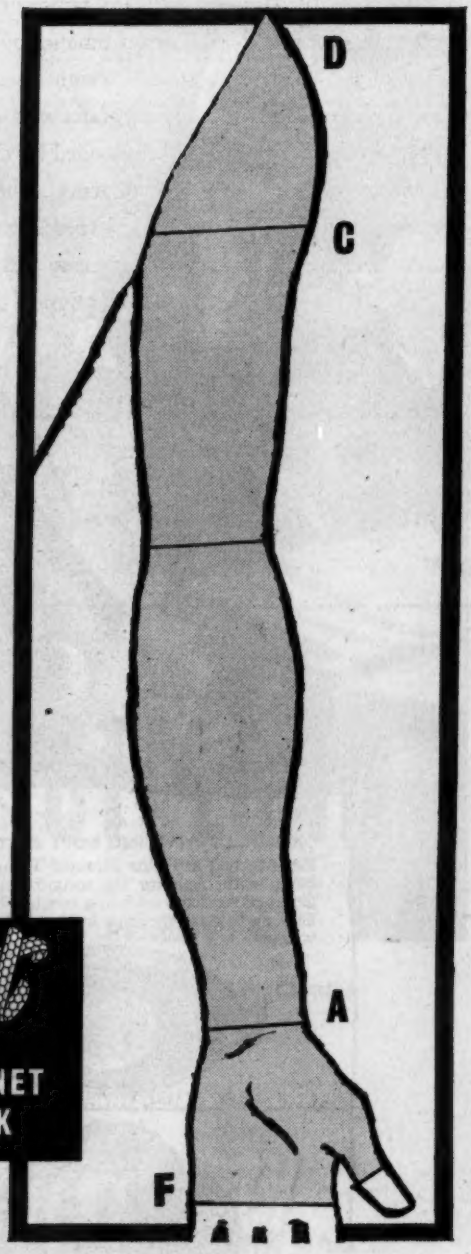

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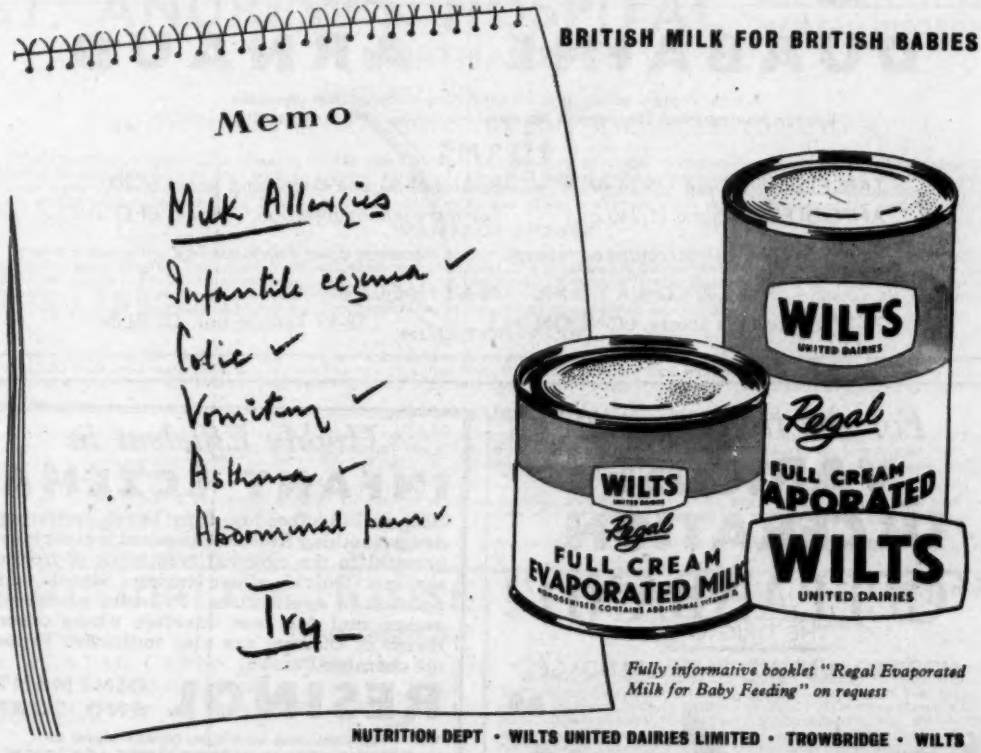

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(UNIVERSITY OF LONDON)
POSTGRADUATE TRAVELLING FELLOWSHIPS

The Governing Body of the British Postgraduate Medical Federation invites applications from registered medical or dental practitioners for a limited number of Postgraduate Travelling Fellowships. The aim of the Fellowships is to enable graduates who are in the course of training as specialists in one of the preclinical or clinical branches of medicine, surgery or dentistry, to obtain experience of the methods of practice, education and research at Universities or other centres in the United Kingdom and abroad. Candidates must be British subjects who are holding an appointment at one of the undergraduate or postgraduate teaching hospitals or medical or dental schools or postgraduate institutes of the University of London. The Fellowships will normally be tenable for 1 year, and the successful candidates will be expected to commence work in September or October, 1958. The value of the Fellowships is not less than £750 p.a. and, in addition, allowances are paid for study abroad, for dependents in the case of married Fellows, and for travelling.

Applications must be submitted before 30th November, 1957, and further information and application forms may be obtained from the Assistant Director, British Postgraduate Medical Federation, Central Office, 18, Guilford-street, London, W.C.1.

BRITISH POSTGRADUATE MEDICAL FEDERATION

(UNIVERSITY OF LONDON). INSTITUTE OF ORTHOPÆDICS, ROYAL NATIONAL ORTHOPÆDIC HOSPITAL, 234, Great Portland-street, London, W.1. Applications are invited for the post of ASSISTANT IN MORBID ANATOMY. The post will provide experience of routine orthopædic pathology and opportunity for research. Interest in experimental work an advantage. Salary £1150–£100–£1750 according to experience. Tenable in the first instance for 1 year, and renewable.

Applications, with the names of 2 referees, should be sent, by 31st October, 1957, to the Dean, from whom further particulars may be obtained.

NAPT SYMPOSIUM MEETINGS

LUNG CARCINOMA. Chairman: N. LLOYD RUSBY, M.A., D.M., F.R.C.P. FRIDAY, 22ND NOVEMBER.

CARDIAC PROBLEMS FOR GENERAL PHYSICIANS. Chairman: K. SHIRLEY SMITH, B.SC., M.D., F.R.C.P. FRIDAY, 6TH DECEMBER.

Both meetings 3.30–6.30 P.M. in Great Hall, B.M.A. House, W.C.1. Tickets, including afternoon tea and sherry, 10s. each.

Details from NAPT, Tavistock House North, W.C.1.

THE UNIVERSITY OF LIVERPOOL.

Applications are invited for the post of Whole-time READER in the Department of Medicine (Professor: The Rt. Hon. Lord Cohen of Birkenhead), duties to commence on 1st January, 1958. The salary will be within the range £1900–£2900 p.a., according to qualifications and experience. The successful candidate will be granted an honorary contract under the Board of Governors of the United Liverpool Hospitals as Consultant Physician of junior status at the Royal Infirmary.

Applications, stating age, academic qualifications and experience, together with the names of 3 referees, should be received not later than 9th November, 1957, by the Registrar, from whom further particulars of the conditions of appointment may be obtained.

UNIVERSITY OF MANCHESTER

DEPARTMENT OF EDUCATION OF THE DEAF

AN INTERNATIONAL CONGRESS ON THE EDUCATIONAL TREATMENT OF DEAFNESS will be held from 15TH TO 23RD JULY, 1958, inclusive, in the University. Members of the Department of Education of the Deaf and delegates from other countries have agreed to demonstrate and discuss the results of recent research on the problems of deafness in childhood. A fee of £3 will be charged to each member of the congress.

Inquiries and requests for forms of application should be addressed to Prof. A. W. G. EWING, Department of Education of the Deaf, The University, Manchester, 13.

UNIVERSITY OF BRISTOL.

Applications are invited for the appointment of LECTURER IN PHYSIOLOGY (Grade II). Applicants should preferably have a medical qualification in which case the present salary scale is £1200–£100–£1600 (Bar) –£100–£1950 according to qualifications and experience. The appointment is subject to F.S.S.U. and a family allowance scheme.

Applications (6 copies), with the names of 3 referees and copies of not more than 3 recent testimonials (if desired) should be forwarded to the undersigned, from whom further particulars may be obtained, not later than 9th November, 1957.

H. C. BUTTERFIELD, Registrar and Secretary.

ROYAL PRINCE ALFRED HOSPITAL. Hallstrom Institute of Cardiology.

Written applications closing 31st December 1957 are called for the position of RESEARCH DIRECTOR of the Hallstrom Institute of Cardiology. Applicants must have had adequate training and practice in a modern cardiological laboratory as well as clinical and administrative ability. Duties will include responsibility for all routine cardiological investigations within the Hospital (daily average 1300 Beds) as well as the initiation and supervision of original research. Adequate medical and lay assistance will be provided and the Institute is fully equipped technically. Commencing salary £A3250 p.a. Initial appointment will be for a period of 3 years.

Further particulars may be obtained from the undersigned.

H. SELLE, General Superintendent.
Royal Prince Alfred Hospital, Missenden Road, Camperdown, N.S.W., Australia.

UNIVERSITY OF BELFAST.

Applications are invited for a LECTURESHIP IN BIOCHEMISTRY. Salary range £900–£50–£1300, and on certain conditions being fulfilled to £1650, plus contributory pension rights under the F.S.S.U. Initial placing on the scale £900–£1300 is dependent on experience and qualifications.

Applications should be received by 1st November, 1957. Further particulars may be obtained from the Secretary, The Queens University of Belfast, Belfast, Northern Ireland.

Hospital Services: Senior Appointments

SOUTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD

requires Part-time CONSULTANT GERIATRICIAN (7 half-days per week) to the Lambeth Group of Hospitals. Duties mainly at South Western Hospital, Stockwell, S.W.17.

Applications by letter (5 copies), giving date of birth, qualifications, experience, and names of 3 referees, to Secretary (S.1), South West Metropolitan Regional Hospital Board, 11A, Portland-place, W.1, by 16th November, 1957. Applicants may visit hospitals by local arrangement.

CHICHESTER GROUP HOSPITAL MANAGEMENT COMMITTEE.

SOUTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD. Anæsthetics. Locum ANÆSTHETIST (5 half-days per week) required pending substantive Consultant appointment. Consultant, Senior Hospital Medical Officer, or Senior Registrar's remuneration according to grading of successful applicant. Group covers Royal West Sussex and St. Richard's Hospitals, Chichester, Bognor Hospital, and Midhurst and Petworth Hospitals.

Inquire of Group Secretary, 174, Broyle-road, Chichester.

LEEDS REGIONAL HOSPITAL BOARD. Whole-time

ASSISTANT PSYCHIATRIST (Senior Hospital Medical Officer scale) for duties at Clifton Hospital, York (1112 Beds), and associated clinics at Harrogate, York and Scarborough. The person appointed may also have duties at Claypenny Hospital for Mental Defectives (1 session per week). Detached 4-bedroomed house available.

Applications (12 copies), stating age, qualifications and details of present and previous appointments with dates, and names and addresses of 3 referees, to the Secretary, Park-parade, Harrogate, by 18th November, 1957.

LEEDS REGIONAL HOSPITAL BOARD. Whole-time

or maximum part-time CONSULTANT in Geriatrics for duties at hospitals in the Bradford A and B Groups. The successful applicant will be responsible for the clinical control of geriatric services in the 2 groups (740 Beds), and will be expected to maintain the present close liaison with general practitioners and the local authority. The appointee will be required to reside in or near Bradford.

Applications (12 copies), stating age, qualifications and details of present and previous appointments with dates, together with the names and addresses of 3 referees, to The Secretary, Park-parade, Harrogate by 18th November, 1957.

MANCHESTER REGIONAL HOSPITAL BOARD. Whole-time

RESIDENT ASSISTANT PHYSICIAN (Senior Hospital Medical Officer) in Infectious Diseases at Ladywell Hospital, Salford. Appointee will act as Physician-Superintendent of the hospital and have charge of the Infectious Diseases Unit there and at Astley Hospital, near Leigh. Wide experience in the diagnosis and treatment of infectious diseases and good experience in general medicine essential. A good family house is available at Ladywell Hospital.

Application forms from the Senior Administrative Medical Officer to the Board, Cheetwood-road, Manchester, 8, to be returned by 28th October, 1957.

NEWCASTLE REGIONAL HOSPITAL BOARD. Main hospitals.

Middlesbrough Maternity (80 Beds); Middlesbrough General (33 gynæcological beds); North Ormesby (25 gynæcological beds); Hemlington (20 gynæcological beds). CONSULTANT OBSTETRICIAN AND GYNÆCOLOGIST. Whole-time or maximum part-time for 9 notional half-days per week for Tees-side and Cleveland groups of hospitals. Appointee will be 1 of a team of 3 and will be required to reside near his main hospital South of River Tees.

Applications, together with names and addresses of 3 referees, to Senior Administrative Medical Officer, Regional Hospital Board, Benfield-road, Newcastle upon Tyne, 6, within 28 days.

NORTH EAST METROPOLITAN REGIONAL HOSPITAL BOARD.

Full-time CONSULTANT PSYCHIATRIST to Runwell Hospital, near Wickford, Essex, with clinics in Southend-on-Sea Group of Hospitals. House available on estate.

Part-time CONSULTANT PSYCHIATRIST to South East Essex Child Guidance Clinic, 119–121, Honeypot-lane, Basildon, for 2 sessions a week. (New clinic in developing area.) Further particulars on application.

Full-time Assistant Psychiatrist (Senior Hospital Medical Officer grade) at Severalls Hospital, Colchester, Essex, with attendance at clinics. Non-resident.

Applications (6 copies), stating post concerned, and names of 3 referees, should reach the Secretary, 11A, Portland-place, London, W.1, by Saturday, 16th November.

NORTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD.

1. CONSULTANT OBSTETRICIAN AND GYNÆCOLOGIST, 4 half-days a week—2 half-days at King Edward Memorial Hospital, Ealing, W.13 (145 Beds), and 2 half-days at Perivale Maternity Hospital, Western-avenue, Greenford, Middlesex (51 Beds).

Applications before 18th November, 1957.

2. CONSULTANT SURGEON, whole-time or maximum sessions, Barnet General Hospital, Wellhouse-lane, Barnet (461 Beds). Successful candidate required to live within easy reach of the Hospital.

Applications before 21st November, 1957.

Hospitals may be visited by direct appointment.

Application forms obtainable from and returnable to Secretary, North West Metropolitan Regional Hospital Board, 11A, Portland-place, W.1.

SCOTLAND. EASTERN AND SOUTH-EASTERN REGIONAL HOSPITAL BOARDS. Radiology. Applications are invited for the appointment of a Whole-time RADIOLOGIST (Consultant) to undertake duties in the Dundee General Hospitals and in Fife. The person appointed will be based on Dundee and although initially his duties will be confined to the Dundee General Hospitals (Dundee Royal Infirmary and Maryfield Hospital—General Teaching Hospitals associated with the University of St. Andrews) he may be required to devote a substantial proportion of his time—but not more than half—to radiological duties in hospitals in the Eastern half of the County of Fife.

Forms of application and further particulars from the Secretary, Eastern Regional Hospital Board, 430, Blackness-road, Dundee, with whom applications must be lodged not later than 12th November, 1957.

SCOTLAND. SOUTH-EASTERN REGIONAL HOSPITAL BOARD. Locum Tenens E.N.T. SURGEON (Consultant or Senior Registrar), duties mainly in the Edinburgh Northern Group of Hospitals.

Apply, giving qualifications and names of 2 referees, to the Secretary, 11, Drumsheugh-gardens, Edinburgh, 3.

SCOTLAND. SOUTH-EASTERN REGIONAL HOSPITAL BOARD. Locum Tenens ORTHOPÆDIC SURGEON (Consultant or Senior Hospital Medical Officer), whole or part-time, for duty in hospitals in Fife; immediate vacancy.

Apply, giving qualifications and names of 2 referees, to the Secretary, 11, Drumsheugh-gardens, Edinburgh, 3.

SCOTLAND. WESTERN REGIONAL HOSPITAL BOARD. Applications are invited for the appointment of CONSULTANT E.N.T. SURGEON at the Royal Infirmary, Glasgow. The appointment will be part-time on the basis of 8 notional half-days per week.

Applications (16 copies), stating date of birth, qualifications, experience, present appointment, and the names of 3 referees, to reach the Secretary, Western Regional Hospital Board, 64, West Regent-street, Glasgow, C.2, not later than 30 days after the publication of this advertisement.

SHEFFIELD REGIONAL HOSPITAL BOARD. Maximum Part-time CONSULTANT RADIOLOGIST required for the Rotherham Group of hospitals.

Application form and further details from the Senior Administrative Medical Officer, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield. Forms to be returned by 9th November, 1957.

SHEFFIELD REGIONAL HOSPITAL BOARD. Maximum part-time CONSULTANT NEUROSURGEON required with main duties at the Derby Group of Hospitals.

Application forms and further details from the Senior Administrative Medical Officer, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield. Forms to be returned by 16th November, 1957.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD. BRISTOL MENTAL HOSPITALS. Applications are invited for the appointment of a Whole-time CONSULTANT PSYCHIATRIST to the Bristol Clinical Area. The successful candidate will work mainly at the Bristol Mental Hospital, Fishponds, but may be required to visit other hospitals in the clinical area as determined by the Regional Board from time to time. No house is available but there may be a small flat at Fishponds Hospital.

Applications (12 copies), stating date of birth, qualifications and experience, together with the names and addresses of 2 referees, should be sent to the Secretary of the Regional Hospital Board, 27, Tyndalls Park-road, Bristol, 8, not later than 9th November, 1957.

NORTHERN IRELAND HOSPITALS AUTHORITY. Applications are invited for a whole-time post as CONSULTANT RADIOLOGIST at hospitals managed by the Belfast Hospital Management Committee. The terms and conditions will be in accordance with the application of the Spens Report to Northern Ireland.

Applications to be made on a form obtainable (with further particulars) from the Secretary, Northern Ireland Hospitals Authority, 44–46, Queen-street, Belfast, and to be returned not later than 4th November, 1957.

U.S.A. NORTH CAROLINA SANATORIUM, McCain, NORTH CAROLINA, U.S.A. Required, PHYSICIANS for full-time employment in 600-Bed Chest Disease Hospital. Salary: Physician I, $7884–$9396; Physician II, $9360–$11,040. Attractive living accommodations for family and single persons at reasonable cost. Hospital affiliated in residency training programmes in medicine and surgery. Located in Central North Carolina, within easy driving range of mountain and seashore resort areas. Year round mild climate. Liberal vacation and sick leave. Retirement and insurance programmes available. Must speak English. Appointments available for 1st January and 1st July, 1958.

Write: Assistant Medical Director.

Hospital Services: Junior Appointments

ALBERT DOCK ORTHOPÆDIC AND FRACTURE HOSPITAL, Alnwick-road, E.16. SEAMEN'S HOSPITAL GROUP. SENIOR HOUSE OFFICER for Receiving Room duties required on 17th November. Post, which is normally resident, is recognised by the Royal College of Surgeons, and provides excellent experience in a wide variety of traumatic conditions received from the adjacent dockland and from shipping in the Port of London. Salary £819 10s.

Applications, stating age, nationality, qualifications and experience, with the names of 2 recent referees, should be sent to the Secretary, Dreadnought Seamen's Hospital, Greenwich, S.E.10, not later than 2nd November.

DREADNOUGHT SEAMEN'S HOSPITAL, Greenwich, S.E.10. HOUSE PHYSICIAN (preregistration) required on 20th November.

Applications, stating age, nationality, qualifications and experience with the names of 3 recent referees, should be sent to the Secretary at the above address not later than 2nd November.

EASTERN HOSPITAL (Fevers), London, E.9. Registered HOUSE PHYSICIAN. Duties may include some work in Chest Unit. Facilities for postgraduate study for higher qualifications.

Apply, Group Secretary, Hackney Hospital, E.9.

HAMMERSMITH HOSPITAL AND POSTGRADUATE MEDICAL SCHOOL, Ducane-road, London, W.12. Whole-time NON-RESIDENT SENIOR REGISTRAR (Anæsthetics) required. Post vacant mid-January.

Applications, stating age, qualifications, experience, names of 2 referees, to Secretary, Board of Governors by 30th October, 1957.

HAMPSTEAD GENERAL HOSPITAL, Haverstock-hill, N.W.3. (Royal Free Hospital Group.) Applications are invited for the pre-registration post of HOUSE PHYSICIAN, vacant 15th November, 1957, tenable for a period of 6 months.

Application forms may be obtained from the Secretary, to whom they should be returned, together with copies of 3 recent testimonials, by 25th October, 1957.

HAMPSTEAD GENERAL HOSPITAL, Haverstock-hill, N.W.3. ROYAL FREE HOSPITAL GROUP. Applications are invited from registered medical practitioners for the post of RESIDENT CASUALTY OFFICER (graded as Senior House Officer). Salary £745 p.a. Tenable for a period of 6 months from the 1st December, 1957, at the main Outpatient Department, Bayham-street, N.W.1.

Application forms may be obtained from the Secretary, to whom they should be returned, together with copies of 3 recent testimonials, by 1st November, 1957.

HOSPITAL OF ST. JOHN AND ST. ELIZABETH, 60, Grove End-road, London, N.W.8. Required to commence on Monday, 2nd December, Full-time SURGICAL REGISTRAR (Male). The possession of the Diploma of one of the Royal Colleges is desirable. Honorarium at the rate of £850 p.a. Appointment will be for a period of 12 months.

Further particulars may be obtained from the Secretary to whom applications, with names of 3 referees, should be sent on or before Tuesday, 5th November.

HOSPITAL OF ST. JOHN AND ST. ELIZABETH, 60, Grove End-road, London, N.W.8. Applications are invited from preregistration or registered medical practitioners (Male) for the appointment of HOUSE SURGEON, to become vacant on Thursday, 7th November. This post is recognised for purposes of the F.R.C.S. (Eng.). Appointment will be for a period of 6 months. National Health Service salary.

Applications should reach the Secretary on or before Wednesday, 23rd October, together with copies of 3 recent testimonials.

LAMBETH HOSPITAL, Brook-drive, S.E.11. South West METROPOLITAN REGIONAL HOSPITAL BOARD. Applications are invited for the appointment of Part-time OPHTHALMIC REGISTRAR (6 sessions per week) for duties in the Ophthalmic Unit which is linked with the Royal Eye Hospital. Vacant 1st January, 1958. The appointment is for 2 years, but is subject to review at the end of the first year.

For form of application apply to the Secretary, Lambeth Group H.M.C., Renfrew-road, S.E.11, to whom completed forms should be returned not later than 2nd November, 1957.

LONDON CHEST HOSPITAL. Hospitals for Diseases OF THE CHEST. 2 vacancies occur 1st December, 1957, for RESIDENT HOUSE PHYSICIAN. Appointment for 6 months, 4 in London, 2 at the Country Branch, near Letchworth, and posts graded as House Officer. Duties include work in the Outpatient Department and special clinics, as well as in wards.

Applications, stating date of birth, qualifications with dates, and previous appointments held, with copies of 3 testimonials, should reach the undersigned not later than 24th October.

THOMAS BROWN, House Governor.

London Chest Hospital, E.2.

MEMORIAL HOSPITAL, Shooters-hill, S.E.18. SENIOR HOUSE OFFICER (Anæsthetics). Vacant shortly. The post provides good experience and is recognised for F.F.A.R.C.S. and D.A. 6 months resident appointment and may then be renewed.

Apply to Group Secretary, Memorial Hospital, Woolwich, S.E.18.

HACKNEY HOSPITAL, London, E.9. (General, 841 Beds.) SENIOR HOUSE OFFICER (obstetrics and gynæcology). Resident post, vacant 19th December. Recognised for M.R.C.O.G.

Apply Secretary, above address, by 28th October.

LEWISHAM HOSPITAL, London, S.E.13. Applications are invited for the post of SENIOR HOUSE OFFICER (Anæsthetics), vacant immediately and tenable for 1 year. Recognised for the D.A. and F.F.A.R.C.S. Salary £819 10s. p.a., less £150 for residential emoluments.

Applications, stating age, qualifications and experience, with copy testimonials or names of referees, to the Group Secretary, Lewisham Hospital, S.E.13.

MIDDLESEX HOSPITAL, W.1. Applications invited for post of REGISTRAR in the Department of X-ray Diagnosis.

Rules and application forms obtainable from Deputy Superintendent should be returned, naming 2 referees, by 6th November.

MIDDLESEX HOSPITAL, W.1. Applications invited for post of SENIOR REGISTRAR in the Department of X-ray Diagnosis now vacant. A second vacancy will probably be advertised shortly.

Rules and application forms obtainable from Deputy Superintendent should be returned, naming 2 referees, by 6th November.

MILE END HOSPITAL, Bancroft-road, London, E.1. (484 Beds.) HOUSE PHYSICIAN (pre- or post-registration), post vacant 19th November, 1957.

Application forms, obtainable from Physician-Superintendent, to be returned by 1st November, 1957, with copies of not more than 3 testimonials.

NORTH MIDDLESEX HOSPITAL, Edmonton, N.18. HOUSE SURGEON (pre- or post-registration), resident, required for 1st December for 6 months. Duties mainly general surgery, with some E.N.T. surgery. Post recognised for F.R.C.S.

Applications, stating age, nationality, qualifications, experience, with copies of recent testimonials, to Secretary of Hospital, by 30th October.

NORTH MIDDLESEX HOSPITAL, Edmonton, N.18. RESIDENT HOUSE PHYSICIAN, post-registration, required for 1st December for 6 months. General medicine.

Applications, stating age, nationality, qualifications, experience, with copies of recent testimonials, to Secretary of Hospital, by 30th October.

NORTH MIDDLESEX HOSPITAL, Edmonton, N.18. RESIDENT HOUSE SURGEON (general, orthopædic and traumatic surgery), pre- or post-registration, required for 6 months. Post recognised for F.R.C.S.

Applications, stating age, nationality, qualifications, experience, with copies of recent testimonials, to Secretary of Hospital.

PADDINGTON GENERAL HOSPITAL, Harrow-road, W.9. Applications are invited for the undermentioned posts commencing 1st December, 1957. Preference will be given to preregistration candidates where appropriate :—

2 HOUSE SURGEONS (general surgery). Preregistration posts. Recognised for F.R.C.S.

2 HOUSE SURGEONS (obstetrics and gynæcology). 1 preregistration post. Both recognised for M.R.C.O.G. in Obstetrics.

4 HOUSE PHYSICIANS (general medicine). Preregistration posts.

Applications, stating age, qualifications, medical school, experience, together with names and addresses of 2 referees, to reach Hospital Secretary, by 1st November, 1957.

PADDINGTON GENERAL HOSPITAL, Harrow-road, W.9. (582 Beds.) Applications are invited for the post of REGISTRAR (general medicine), whole-time, non-resident. The appointment offers experience in all branches of medical work and the duties include supervision and teaching of medical clerks from St. Mary's Hospital Medical School. Hospital may be visited by direct appointment.

Application forms obtainable from and returnable to Secretary to Committee, Paddington Group Hospital Management Committee, Harrow-road, W.9, by 31st October.

PRINCE OF WALES'S GENERAL HOSPITAL, N.15. Applications are invited for the appointment of RESIDENT SENIOR HOUSE PHYSICIAN (third post) to the above Hospital for a period of 6 months from 3rd December, 1957.

Application form from Secretary, Tottenham Group Hospital Management Committee, The Green, N.15, to be returned by 1st November, 1957.

PRINCE OF WALES'S GENERAL HOSPITAL, N.15. Applications are invited for the appointment of RESIDENT JUNIOR HOUSE SURGEON for Casualty (preregistration first or second post) to the above Hospital for a period of 6 months, vacant 27th November, 1957.

Application form from Secretary, Tottenham Group Hospital Management Committee, The Green, N.15, to be returned by 1st November, 1957.

ROYAL FREE HOSPITAL. Applications are invited for the post of RESIDENT PATHOLOGIST (House Officer), vacant immediately, from registered Men and Women practitioners. The post is for 6 months, renewable for a further 6 months. Salary and conditions of service in accordance with the scale laid down by the Ministry of Health for House Officers.

Application forms may be obtained from the Secretary, Royal Free Hospital, Gray's Inn-road, W.C.1, to whom they should be returned as soon as possible.

ST. ANN'S GENERAL HOSPITAL, N.15. Applications are invited for the appointment of RESIDENT HOUSE PHYSICIAN (Senior House Officer) to Pædiatric and Infectious Diseases Department at above Hospital for a period of 6 months from 3rd December, 1957.

Application form from Secretary, Tottenham Group Hospital Management Committee, The Green, N.15, to be returned by 1st November, 1957.

ROYAL NORTHERN HOSPITAL, Holloway-road, London, N.7. CLINICAL ASSISTANT (part-time) required for Dental Department (General Practitioner grade) 4 sessions per week.

Application forms and further particulars from Hospital Secretary.

ST. CHARLES' HOSPITAL, Ladbroke-grove, W.10. (576 Beds.) Applications are invited for the post of SENIOR HOUSE OFFICER (pædiatrics, geriatrics, and general wards).

Applications, stating age, qualifications, experience, together with the names and addresses of 2 referees, to be forwarded to Hospital Secretary immediately.

ST. FRANCIS' HOSPITAL, Constance-road, East Dulwich, S.E.22. Applications are invited from general practitioners for appointment to paid CLINICAL ASSISTANTSHIPS for 2 to 4 sessions a week, in the Geriatric Unit, St. Francis' Hospital.

Applications, giving details of qualifications and experience, should be sent to the Group Secretary, Camberwell Hospital Management Committee, Dulwich Hospital, S.E.22, to reach him by 31st October, 1957.

ST. GILES' HOSPITAL, Camberwell, S.E.5. House SURGEON (casualty duties, with some general surgical, E.N.T. and eye beds). Recognised preregistration post.

Applications, with copy testimonials or names of referees, to Group Secretary, Camberwell Hospital Management Committee, Dulwich Hospital, East Dulwich-grove, S.E.22.

ST. MARY'S HOSPITAL, CHILDREN'S DEPARTMENT, PRINCESS LOUISE KENSINGTON HOSPITAL FOR CHILDREN, St. Quintin-avenue, W.10. HOUSE OFFICER required (second or third post). Medical. Vacant 1st December, 1957. Preregistration (second post), candidates considered. Recognised for the D.C.H.

Applications to undersigned not later than Monday, 28th October, 1957. A. C. YOUNG, Secretary.

ST. MARY'S HOSPITAL, Paddington, W.2. Registrar (whole-time, non-resident) in General Medicine required to undertake work in the Casualty and Outpatient Departments, as well as having certain inpatient duties. The appointment will be for a first period of 12 months, as from 1st January, 1958.

Applications, stating nationality, date of birth, permanent address, qualifications with dates, details and gradings of previous and present appointments, together with the names and addresses of 3 referees, should reach ALAN POWDITCH, House Governor, not later than 5th November, 1957.

ST. MARY'S HOSPITAL, Paddington, W.2. Resident HOUSE PHYSICIAN to the Neurological, Dermatological and Venereological Departments required, for which either preregistration interns seeking their second House Officer appointment, or postregistration candidates are eligible to apply. The appointment is for a period of 6 months with effect from 1st December, 1957.

Applications, stating nationality, date of birth, permanent address, qualifications with dates, details and gradings of previous and present appointments, together with the names and addresses of 3 referees, should reach ALAN POWDITCH, House Governor, by 29th October, 1957.

ST. MARY'S HOSPITAL, Paddington, W.2. Clinical PATHOLOGIST required for a period of 8 months, with effect from 1st December, 1957. Remuneration at "Senior House Officer" rates. (First 2 months non-resident, remaining six months resident.) Applicants should have held 2 House Officer appointments at this Hospital or another Hospital approved by the Board of Governors and preference will be given to those intending to specialise in pathology.

Applications, stating nationality, date of birth, permanent address, qualifications with dates, details and gradings of previous and present appointments, together with the names and addresses of 3 referees, should reach ALAN POWDITCH, House Governor, not later than 5th November, 1957.

ST. NICHOLAS HOSPITAL, Plumstead, S.E.18. SENIOR HOUSE OFFICER (Casualty Department). Vacant 27th November. Recognised for F.R.C.S. 6 months resident appointment and may then be renewed for a further period.

Apply to Group Secretary, Memorial Hospital, Woolwich, S.E.18.

ST. STEPHEN'S HOSPITAL, Chelsea, S.W.10. House SURGEON (obstetrics and gynæcology). Second post. Resident. Vacancy 21st November. Post recognised for D.Obst.R.C.O.G.

Applications, naming 2 referees, to be submitted to the Medical Superintendent, within 14 days.

ST. STEPHEN'S HOSPITAL, Chelsea, S.W.10. House PHYSICIAN (pre-registration). Resident. Vacancy mid-November, 1957.

Applications, naming 2 referees, to Medical Superintendent within 14 days.

ST. STEPHEN'S HOSPITAL, Chelsea, S.W.10. House PHYSICIAN for duty in Rheumatism Unit. Resident. This post offers valuable experience in general medicine and specialised experience in rheumatic and connective tissue diseases and is very suitable for candidates wishing to take membership. Vacancy early December.

Applications, naming 2 referees, to Medical Superintendent within 14 days.

ST. TERESA'S MATERNITY HOSPITAL, Wimbledon, S.W.20. (60 Beds.) Applications are invited from fully registered medical practitioners for the appointment of RESIDENT OBSTETRIC HOUSE OFFICER for 6 months in the first instance, commencing about 31st December. Salary £467 10s.–£819 10s. p.a., according to experience. Emoluments deducted according to usual scale. Self-contained flat available in the Hospital grounds. The appointment is recognised for the D.Obst.R.C.O.G.

Applications, stating age, qualifications, nationality and experience and 2 recent testimonials, to the Medical Secretary by 7th November, 1957.

ST. THOMAS'S HOSPITAL, London, S.E.1. Obstetric HOUSE PHYSICIAN at the General Lying-in Hospital, York-road, S.E.1, for a period of 6 months from 1st January, 1958. Resident. Approved service for M.R.C.O.G.

Applications, from full registered medical practitioners only, to the Clerk of the Governors by 31st October, 1957, naming 2 referees.

ST. THOMAS'S HOSPITAL, London, S.E.1. Registrar to the Department of Venereal Diseases required immediately, for a period of 1 year in the first instance, to carry out 8 half-day sessions per week.

Applications, naming 2 referees, to the Clerk of the Governors by 31st October, 1957.

ST. THOMAS'S HOSPITAL, London, S.E.1. Junior HOSPITAL MEDICAL OFFICER to the Department of Venereal Diseases required immediately, for a period of 1 year in the first instance to carry out 8 half-day sessions per week.

Applications, naming 2 referees, to the Clerk of the Governors by 31st October, 1957.

TAVISTOCK CLINIC, 2, Beaumont-street, London, W.1. Applications are invited for the appointment of SENIOR PSYCHIATRIC REGISTRAR in the Department for Children and Parents. At least 1 year's previous experience in child psychiatry essential. Experience in pædiatrics and/or some training in psychoanalysis an advantage. Clinic may be visited by direct appointment.

Application forms obtainable from and returnable to Secretary to Committee, Paddington Group Hospital Management Committee, Harrow-road, W.9, by 31st October.

THE HOSPITAL FOR SICK CHILDREN, Great Ormond-street, London, W.C.1. There will be vacancies on 15th January, 1958, for the following Senior House Officers:

2 HOUSE PHYSICIANS.
2 HOUSE SURGEONS.

Further particulars and form of application, which must be returned not later than 11th November, 1957, are obtainable from the undersigned.

H. F. RUTHERFORD, House Governor and Secretary.

THE HOSPITAL FOR SICK CHILDREN, Great Ormond-street, London, W.C.1. There will be a vacancy on 9th January, 1958, for a REGISTRAR in Clinical Pathology (full-time).

Further particulars and form of application, which must be returned not later than 11th November, 1957, are obtainable from the undersigned.

H. F. RUTHERFORD, House Governor and Secretary.

UNIVERSITY COLLEGE HOSPITAL, Gower-street, W.C.1. Applications are invited for the appointment of RESIDENT ASSISTANT PHYSICIAN (graded Senior Registrar). This post is whole-time and resident.

Applications, with names of 2 referees, to Administrator and Secretary by 2nd November, 1957.

WESTMINSTER HOSPITAL, St. John's-gardens, S.W.1. Applications invited for 2 posts of SENIOR HOUSE OFFICER to Anæsthetics Department for 1 year. Posts vacant from 1st November, 1957, and 1st January, 1958.

Applications (9 copies), with names of 2 referees, to House Governor by 29th October.

WESTMINSTER HOSPITAL, St. John's-gardens, S.W.1. Applications invited for post of SURGICAL REGISTRAR for 1 year in first instance. Post vacant now.

Applications (6 copies), with names of 2 referees, to House Governor by 2nd November.

WHIPPS CROSS HOSPITAL, London, E.11. Leyton-STONE (NO. 10) HOSPITAL GROUP. Applications are invited for the post of SENIOR HOUSE OFFICER (Casualty Officer) at above Hospital. This post, which is recognised by the Royal College of Surgeons for 6 months' casualty training under the Fellowship Regulations, becomes vacant on 4th November, 1957.

Application forms from the Hospital Secretary to be returned by 28th October, 1957.

WHITTINGTON HOSPITAL, London, N.19. Pædiatric REGISTRAR required. Vacant 1st January, 1958. Unit contains 53 Beds in addition to 64 neo-natal cots. Post recognised for M.D., and D.C.H. Hospital may be visited by appointment with the Medical Superintendent.

Application forms obtainable from and returnable to the Secretary, Archway Group Hospital Management Committee, 46, Cholmeley-park, N.6, by 29th October, 1957.

WOOLWICH GROUP HOSPITAL MANAGEMENT COMMITTEE.

SENIOR HOUSE OFFICER (Obstetrics). British Hospital for Mothers and Babies, Samuel Street, Woolwich. Recognised for M.R.C.O.G. or D.Obst.R.C.O.G. Vacant end of November.

HOUSE SURGEONS (Gynæcology and Obstetrics). Two posts vacant during December. One at St. Nicholas Hospital, Plumstead, recognised for D.Obst.R.C.O.G. or 3 months Obstetrics, 3 months Gynæcology for M.R.C.O.G. One at Memorial Hospital, recognised for M.R.C.O.G. (6 months Gynæcology). Small Obstetric Unit providing good experience.

Applications to Group Secretary, Memorial Hospital, Woolwich, S.E.18

BARNSTAPLE. NORTH DEVON INFIRMARY. (105 Beds.) HOUSE SURGEON required; recognised preregistration appointment.

Applications to Group Secretary, 19, Alexandra-road, Barnstaple.

BARROW-IN-FURNESS. NORTH LONSDALE HOSPITAL. Applications are invited for the resident post of HOUSE OFFICER (surgical) (recognised for preregistration) at the above Hospital. Post available immediately. Recognised for F.R.C.S.

Applications to the Group Secretary, Barrow and Furness Hospital Management Committee, 105, Abbey-road, Barrow-in-Furness.

ABERDEEN GENERAL HOSPITALS BOARD OF MANAGEMENT. Applications are invited for the post of REGISTRAR in Surgery with main duties in the Aberdeen Royal Infirmary. The post is a whole-time one and is non-resident. Salary and conditions of service are in accordance with the terms issued by the Department of Health for Scotland.

Applications, giving details of qualifications and experience, with the names of 2 referees, should be lodged with the Secretary, Aberdeen General Hospitals, P.O. Box No. 92, 62, Queen's-road, Aberdeen, within 14 days of the appearance of this advertisement.

ASHFORD HOSPITAL, Ashford, Middlesex. North WEST METROPOLITAN REGIONAL HOSPITAL BOARD. RESIDENT MEDICAL REGISTRAR required at above Hospital for General Medical Unit. Post vacant 18th November, 1957. Hospital may be visited by direct appointment with the Medical Director.

Application forms obtainable from and returnable to Secretary, Staines Group Hospital Management Committee, Ashford Hospital, Ashford, Middlesex, by 29th October.

BANGOR. CAERNARVON AND ANGLESEY GENERAL HOSPITAL. Applications are invited for the post of HOUSE PHYSICIAN at the above Hospital. The appointment is for a period of 6 months. Salary and conditions of service in accordance with those approved by the Ministry of Health.

Applications, stating age, qualifications and experience, together with the names and addresses of 2 referees, to be forwarded to the Group Secretary, Caernarvon and Anglesey Hospital Management Committee, Plas Gwyn, Ffriddoedd-road, Bangor, within 10 days of the appearance of this advertisement.

BARNSLEY CHEST SERVICE. Sheffield Regional HOSPITAL BOARD. Whole-time REGISTRAR (chest diseases) required. Single accommodation available at Wathwood Hospital. Duties at the Hospital and Barnsley Clinics under the supervision of the Consultant. Appointment for 1 year in first instance.

Apply to Secretary, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, by 28th October, 1957, giving age, nationality, qualifications, present and previous appointments with dates, naming 3 referees.

BEVERLEY, YORKSHIRE. WESTWOOD HOSPITAL. (229 acute beds.) ORTHOPÆDIC HOUSE SURGEON (first, second or third post), vacant now. Offers good opportunity for general experience in busy acute general hospital. Approved preregistration post. Fully registered practitioners may apply. Recognised for F.R.C.S.

Apply Group Secretary.

BEVERLEY, YORKSHIRE. WESTWOOD HOSPITAL. (229 Beds.) HOUSE PHYSICIAN (House Officer of Senior House Officer grading according to experience).

Apply Group Secretary.

BEDFORD GENERAL HOSPITAL. (436 Beds.) Locum MEDICAL REGISTRAR required from 23rd October.

Applications to Group Secretary, Bedford Group Hospital Management Committee, 3, Kimbolton-road, Bedford (Tel. Bedford 5401).

BEDFORD GENERAL HOSPITAL. (436 Beds.) Ortho-PÆDIC HOUSE SURGEON required beginning of November. Pre- or post-registration; recognised for F.R.C.S. Post offers wide experience in a busy specialist orthopædic and traumatic unit.

Inquiries and applications, with copies of 2 recent testimonials, to be sent immediately to Group Secretary, Bedford Group Hospital Management Committee, 3, Kimbolton-road, Bedford.

BEDFORD GENERAL HOSPITAL. (436 Beds.) House SURGEON required. Pre- or post-registration; recognised for F.R.C.S. Vacant beginning of November. Post offers exceptional opportunities for general experience in busy acute surgical units.

Inquiries and applications, with copies of 2 recent testimonials, to be sent immediately to Group Secretary, Bedford Group Hospital Management Committee, 3, Kimbolton-road, Bedford.

BIRMINGHAM ACCIDENT HOSPITAL, Bath-row, BIRMINGHAM, 15. (215 Beds and 8 House Surgeons.) HOUSE SURGEONS (resident). Vacant December. Hospital largest traumatic unit in country and treats over 50,000 new patients each year. Recognised for purpose of Casualty by R.C.S. (Eng.). Teaching programme by consultant staff. 6-month appointment, some of which may be spent in 42-bedded Medical Research Council's Burns Unit.

Apply, naming 2 referees, to Administrator within 6 days.

BIRMINGHAM, 18. DUDLEY ROAD HOSPITAL. (780 Beds.) SENIOR HOUSE OFFICER (resident or non-resident) for Casualty Department (40,000 attendances a year), vacant 14th November, 1957. Post recognised for F.R.C.S. and tenable for 6 or 12 months.

Applications, with copies of 2 recent testimonials, to Group Secretary.

BIRMINGHAM. THE UNITED BIRMINGHAM HOSPITALS. THE CHILDREN'S HOSPITAL, Ladywood-road, BIRMINGHAM, 16. Applications are invited for the post of RESIDENT MEDICAL OFFICER, second of 2 (Senior House Officer grade), vacant 1st January, 1958, for 1 year. Main duty to take charge of Infants Block (66 Cots). Valuable opportunity for further study of disease of infancy, some previous experience of which is desirable. M.R.C.P. preferred.

Forms of application available from the House Governor and should be returned to him by 9th November, 1957.

G. A. PHALP, Secretary to the Board of Governors.

BISHOP'S STORTFORD, HERTFORDSHIRE. HERTS AND ESSEX GENERAL HOSPITAL. (386 Beds.) SENIOR HOUSE OFFICER (surgical) required for general and orthopædic surgical duties. Salary £819 10s. p.a., less £150 in respect of residential emoluments.

Further particulars from, or applications with names of 2 referees to, the Hospital Secretary.

BISHOP'S STORTFORD AND DISTRICT HOSPITAL, Rye-street, BISHOP'S STORTFORD, HERTFORDSHIRE. (67 Beds—Medical, Surgical and Maternity.) Applications are invited from registered medical practitioners for the post of RESIDENT SENIOR HOUSE OFFICER (Male). Salary £819 10s. p.a., less £150 for residential emoluments. To commence 1st November or as soon thereafter as possible.

Applications, stating age, nationality, qualifications and experience, with copies of recent testimonials or names of referees, to Hospital Secretary, Herts and Essex General Hospital Bishop's Stortford, Herts.

BLACKBURN AND DISTRICT HOSPITAL MANAGEMENT COMMITTEE. JUNIOR HOSPITAL MEDICAL OFFICER required mid-November for established Geriatric Department under control of Consultant Geriatrician. There are 360 geriatric beds at Queen's Park Hospital, Blackburn, Springfield Hospital, Blackburn, and Clitheroe Hospital, Clitheroe. Accommodation for married man may be available if required.

Applications, with names of 2 referees, to Group Secretary, Hospital Management Committee Office, Royal Infirmary, Blackburn.

BLACKBURN ROYAL INFIRMARY (262 general beds). BLACKBURN AND DISTRICT HOSPITAL MANAGEMENT COMMITTEE. HOUSE SURGEON required 22nd November, 1957. Post recognised for F.R.C.S. and approved for preregistration purposes.

Applications to Group Secretary, Hospital Management Committee Office, Royal Infirmary, Blackburn, Lancs.

BOURNEMOUTH. ROYAL VICTORIA HOSPITAL, Shelley-road. BOURNEMOUTH AND EAST DORSET HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the appointment of GENERAL HOUSE SURGEON. The appointment is recognised for the F.R.C.S. examination and for preregistration purposes and becomes vacant on 21st November, 1957.

Applications to the Hospital Secretary.

BOURNEMOUTH. ROYAL VICTORIA HOSPITAL, Shelley-road. BOURNEMOUTH AND EAST DORSET HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the appointment of RESIDENT SENIOR HOUSE OFFICER (Anæsthetics). The post is recognised for the D.A. and F.F.A.R.C.S., becomes vacant on 3rd December, 1957, and is normally tenable for 12 months. Experience with Thoracic Unit available.

Applications to the Hospital Secretary.

BOURNEMOUTH (near). CHRISTCHURCH HOSPITAL, CHRISTCHURCH, HANTS. HOUSE PHYSICIAN (Preregistration Intern) required for general medicine for post becoming vacant on 17th November, 1957, at the above Hospital of 334 Beds (including 79 acute medical, 34 pædiatric, 56 surgical, 6 chest diagnostic, and a geriatric ward). Duties also include attendance at outpatient clinics at the Royal Victoria Hospital, Boscombe.

Applications to the Hospital Secretary.

BURY ST. EDMUNDS. WEST SUFFOLK GENERAL HOSPITAL. (262 Beds.) Applications are invited for the following posts :—

(*a*) HOUSE OFFICER (Preregistration) or SENIOR HOUSE OFFICER for orthopædic and casualty duties ; recognised for F.R.C.S. (surgical) ; vacant early January. A Junior Hospital Medical Officer is also employed.

(*b*) HOUSE PHYSICIANS for (i) general medical duties and (ii) pædiatric and general medical duties ; vacant early December.

(*c*) HOUSE SURGEONS for (i) general surgical and other duties ; and (ii) general surgical (latter recognised for F.R.C.S.) ; vacant early December and early January respectively.

(*d*) HOUSE SURGEON for gynæcological and obstetric duties, recognised for D.Obst.R.C.O.G. ; vacant late December.

(*e*) HOUSE PHYSICIANS (Locum Tenens) for general medical duties for periods mid-October to early November and mid-November to early December.

All posts except (*a*) as shown are recognised for Preregistration, but for post (*d*) considered advisable to have held previous appointment.

Applications to Hospital Secretary with testimonials or names of referees.

BUXTON. DEVONSHIRE ROYAL HOSPITAL. (252 Beds.) Applications are invited for the post of RESIDENT SENIOR HOUSE OFFICER. This Hospital is a large special hospital for the treatment and rehabilitation of all types of locomotor disorders. Duties are mainly medical and include work in the long-stay unit of the Manchester University Rheumatism Research Centre. The Hospital is recognised under the regulations for the Diploma in Physical Medicine, Part II, and the post also offers good medical experience.

Applications, stating age, experience and qualifications, together with the names of 2 persons for reference, to be addressed to the Secretary, Stockport and Buxton Hospital Management Committee, 59B, Shaw-heath, Stockport, immediately.

CARDIFF. UNITED CARDIFF HOSPITALS. Applications are invited for the post of MEDICAL REGISTRAR to the Miners' Chest Diseases Treatment Centre at Llandough Hospital, Penarth, Glam. The Centre caters for all types of chest diseases and it is closely associated with the adjoining Pneumoconiosis Research Unit of the Medical Research Council.

Application forms may be obtained from the Secretary to the Board at Cardiff Royal Infirmary, Cardiff, and should be returned not later than 26th October, 1957.

CARDIFF. THE UNITED CARDIFF HOSPITALS. Applications are invited for the appointment of REGISTRAR to the Orthopædics and Fracture Departments, Cardiff Royal Infirmary, to commence duty as soon as possible.

Application forms are available from the Secretary to the Board, at the Cardiff Royal Infirmary, Newport-road, Cardiff, and should be returned within 14 days of the appearance of this advertisement.

CARDIFF. THE UNITED CARDIFF HOSPITALS. Applications are invited for the post of SENIOR HOUSE OFFICER (Medical) to the Miners' Chest Diseases Treatment Centre at Llandough Hospital, Penarth. The Centre caters for all types of chest diseases and it is closely associated with the adjoining Pneumoconiosis Research Unit of the Medical Research Council.

Application forms are available from the Secretary to the Board at the Cardiff Royal Infirmary, Newport-road, Cardiff, and should be returned within 14 days of the appearance of this advertisement.

CAMBRIDGE. THE UNITED CAMBRIDGE HOSPITALS. REGISTRAR in Infectious Diseases (residence available), Brookfields Hospital, Cambridge, which is the Poliomyelitis Centre for the south-west section of East Anglia and the Infectious Diseases Hospital of the United Cambridge Hospitals. There is also a ward for tuberculosis, and one for general medicine. Appointment for 1 year in first instance, renewable for a second year.

Apply, with full particulars and names of 3 referees, to Secretary, Addenbrooke's Hospital, by 31st October.

CANTERBURY. KENT AND CANTERBURY HOSPITAL (277 Beds). GYNÆCOLOGICAL HOUSE SURGEON required at Highland Court annexe, a unit of 25 gynæcological beds situated 3 miles from the above Hospital, with all ancillary services available. Recognised for M.R.C.O.G. 6 months' appointment. Post vacant early in December, 1957. National Health Service salary and conditions.

Applications, together with copies of 2 recent testimonials, to be addressed to the Hospital Secretary at the above Hospital.

CHELMSFORD. ST. JOHNS' HOSPITAL. (Recognised for M.R.C.O.G.) RESIDENT GYNÆCOLOGICAL HOUSE SURGEON. Appointment to commence as soon as possible. Preference will be given to candidates who intend to obtain the Diploma of Membership of the Royal College of Gynæcologists.

Applications, stating age, nationality, qualifications and experience, together with recent testimonials, should be sent immediately to the Secretary, Chelmsford Group Hospital Management Committee, Chelmsford and Essex Hospital, London-road, Chelmsford.

CHELMSFORD AND ESSEX HOSPITAL. (161 Beds.) Applications are invited for the post of RESIDENT HOUSE SURGEON. Preregistration post. The post will become vacant during the middle of November, and offers good surgical experience. Recognised for the F.R.C.S.

Applications, together with 2 recent testimonials, to the Secretary, Chelmsford Hospital Management Committee, London-road, Chelmsford.

CHELMSFORD HOSPITAL MANAGEMENT COMMITTEE. Resident Locum Tenens REGISTRAR in Surgery required to work at the Chelmsford and Essex Hospital for period 26th October–8th November, inclusive.

Applications to the Secretary, London-road, Chelmsford.

CHERTSEY, SURREY. ST. PETER'S HOSPITAL (late Botley's Park War Hospital). (430 Beds.) ORTHOPÆDIC HOUSE SURGEON (Senior House Officer, or House Officer (Intern) grade). 100 orthopædic beds. Post recognised for F.R.C.S. and Preregistration Service. Salary in accordance with terms and conditions of National Health Service. Post vacant 1st November, 1957.

Applications, together with names and addresses of referees, to be sent to the Physician-Superintendent, St. Peter's Hospital, Chertsey, as soon as possible.

CHESTER. DEVA MENTAL HOSPITAL, Liverpool-road. JUNIOR HOSPITAL MEDICAL OFFICER required. Salary scale £852 10s.–£55–£1182 10s. p.a. Accommodation available for married or single person. All forms of modern treatment given and Psychiatric Outpatient Clinics staffed at local general hospitals. Study facilities.

Apply Medical Superintendent.

CHESTERFIELD. SCARSDALE HOSPITAL. Applications are invited for the post of JUNIOR HOSPITAL MEDICAL OFFICER for Geriatric Unit and for duties at Penmore Hospital. Full Consultant services. Excellent scope for doctor interested in this specialty. House available on service tenancy.

Applications, giving full particulars, with name of 3 referees, to Group Secretary, Chesterfield Hospital Management Committee, at Chesterfield Royal Hospital.

CHICHESTER. ROYAL WEST SUSSEX HOSPITAL (202 acute beds). RESIDENT HOUSE SURGEON required for 6 months' appointment. National salary scales for either provisionally or fully registered practitioners. Post approved for preregistration practitioners and F.R.C.S. 8 residents. Vacant 17th November, 1957.

Applications, stating age, experience, qualifications, with references or names of referees, to Senior Administrative Officer.

DEWSBURY, YORKSHIRE. THE GENERAL HOSPITAL.

HOUSE OFFICER (surgery and E.N.T.).

HOUSE OFFICER (medicine and dermatology).

Applications are invited for the above posts which become vacant on 1st November. Both the appointments are recognised for preregistration.

Applications, stating age and experience, and giving names and addresses of 2 referees, to the Administrative Officer at the Hospital.

EAST GRINSTEAD. QUEEN VICTORIA HOSPITAL. PLASTIC SURGERY AND JAW INJURIES CENTRE. TUNBRIDGE WELLS GROUP HOSPITAL MANAGEMENT COMMITTEE. Applications invited for resident appointment of SENIOR HOUSE OFFICER in Anæsthetics, vacant 7th December, 1957. Duties in anæsthesia for both general and plastic surgery. Post recognised for examinations of D.A. and F.F.A.R.C.S.

Apply, stating qualifications, experience, age, and names of 3 referees, by 11th November, 1957, to Group Secretary, Sherwood Park, Pembury-road, Tunbridge Wells.

COLCHESTER GROUP HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for:—

Essex County Hospital, Colchester, Essex. (189 Beds.) Post of SENIOR HOUSE OFFICER to Casualty and E.N.T. Departments. Post tenable for 6 months or 1 year. Recognised for F.R.C.S.

Applications with copies of 3 testimonials, to Group Secretary, Colchester Hospital Management Committee, 14, Pope's-lane, Colchester, Essex.

CROMER AND DISTRICT HOSPITAL, Norfolk. Applications are invited for the post of RESIDENT MEDICAL OFFICER (Senior House Officer status). Post vacant 1st December, 1957, at a salary of £819 10s. p.a. in accordance with National Hospital Service conditions. This is a busy general hospital of 52 Beds, with an outpatient department where Consultants in all the major specialties hold regular sessions. The appointment thus offers practical experience of an all round kind particularly useful to those contemplating entry into general practice. Residential accommodation is available and occupancy of a very adequate furnished flat at the hospital is a condition of employment in the case of a married man.

Applications, stating age, qualifications, experience, sex, and the names of 2 referees, should be addressed to the Secretary, Cromer and District Hospital, Mill-road, Cromer.

DURHAM COUNTY HOSPITAL. (116 Beds.) Senior HOUSE OFFICER in Orthopædics required immediately. Resident. The County Hospital is the main Orthopædic and Accident Hospital in a busy mining and industrial area. Experience can be obtained in all branches of orthopædics.

Applications, with particulars of previous experience and names of 2 referees, to Group Secretary, Dryburn Hospital, Durham.

DURHAM COUNTY HOSPITAL. (116 Beds.) Resident HOUSE SURGEON required in Orthopædics and Casualty. Post recognised for preregistration purposes. This post offers facilities for good and varied experience in a busy orthopædic and accident hospital which serves a wide mining and industrial area.

Apply, giving age, experience and names of 2 referees, to the Group Secretary, Dryburn Hospital, Durham.

EDGWARE GENERAL HOSPITAL, Edgware, Middlesex. 2 RESIDENT OBSTETRIC HOUSE SURGEONS for above Hospital. Posts vacant 30th November and 5th December, 1957. 6 months' appointments. 1 post recognised for preregistration purposes. Both posts recognised for M.R.C.O.G.

Applications, stating age, qualifications, experience and enclosing copies of up to 3 recent testimonials, to Medical Director of Hospital by 31st October, 1957.

FARNBOROUGH HOSPITAL, Kent. (300 Beds.) 2 House SURGEONS required, 1 from 1st and 1 from 14th December. Recognised for F.R.C.S. Preregistration posts.

Apply, stating age, qualifications with dates, and experience, and naming 3 referees, to Administrative Officer, quoting ref. H.S.

GLASGOW VICTORIA HOSPITALS BOARD OF MANAGEMENT AND THE EXECUTIVE COUNCIL FOR THE CITY OF GLASGOW. Applications are invited for 2 joint appointments as Part-time SENIOR HOUSE OFFICER in General Medicine at the Victoria Infirmary, Glasgow, and Part-time trainee General Practitioner. The appointments will be for 2 years and the successful applicants will spend part of each day in the general medical work of the Victoria Infirmary and part as a trainee general practitioner with a selected principal. The salary for the posts will be £819 10s. for the first year and £850 for the second year. A car allowance may be payable in addition.

Applications, with names of 2 referees, should be sent to the Secretary and Treasurer, Board of Management for Glasgow Victoria Hospitals, 24, St. Vincent-place, Glasgow, C.1, not later than 31st October, 1957.

GLASGOW NORTHERN HOSPITALS BOARD OF MANAGEMENT. Applications are invited for the following posts at Stobhill General Hospital, Glasgow :—

(*a*) SENIOR HOUSE OFFICER in Obstetrics and Gynæcology ;

(*b*) SENIOR HOUSE OFFICER in Anæsthetics.

The appointments will be for 1 year in the first instance.

Applications, stating age, qualifications, experience, present appointment and post applied for, and naming 2 referees, to be lodged with the Secretary, 13, Woodside-place, Glasgow, C.3, by 31st October, 1957.

GLASGOW NORTHERN HOSPITALS. Board of Management. Applications are invited for the post of SENIOR HOUSE OFFICER for duties mainly in Obstetrics at Robroyston Hospital, Glasgow, with a few sessions in Gynæcology at another hospital in Glasgow. The appointment will be for 1 year in the first instance.

Applications, stating age, qualifications, experience and present appointment and naming 2 referees, to be lodged with the Secretary, 13, Woodside-place, Glasgow, C.3, by 24th October, 1957.

GLASGOW. STOBHILL GENERAL HOSPITAL, N.1. Applications are invited for the post of JUNIOR HOSPITAL MEDICAL OFFICER, Male or Female (resident preferred), in the Psychiatric Unit which consists of 170 Beds with 1800 admissions yearly and deals with acute treatable cases; it is recognised for the D.P.M.

Applications, stating age, qualifications and experience and naming 2 referees, should be sent to the Medical Superintendent.

GRIMSBY GENERAL HOSPITAL. Applications are invited for CASUALTY OFFICER (Senior House Officer grade) with some E.N.T. duties. Post vacant in November. Appointment recognised for F.R.C.S. The staffing of the department is a Senior Casualty Officer and 2 Senior House Officers. Up-to-date medical library and reading facilities available.

Applications, with names and addresses of 2 referees, to Hospital Secretary.

GREENOCK. RAVENSCRAIG HOSPITAL (Mental and General). Applications are invited for the post of RESIDENT JUNIOR HOSPITAL MEDICAL OFFICER (Male or Female). The post offers experience in all branches of psychiatry, including modern forms of treatment, and outpatient clinics. Experience is available also in the medical and geriatric wards. The Hospital is recognised for the D.P.M. and facilities will be granted to attend courses in Glasgow. It is probable that married quarters will be available in the near future.

Applications, with full details and the names of 2 referees, to be forwarded to the Physician Superintendent.

HALIFAX. ROYAL HALIFAX INFIRMARY. House PHYSICIAN in General Medicine required. Post vacant 1st November, 1957.

Apply to Group Secretary, Royal Halifax Infirmary, Halifax.

HAREFIELD HOSPITAL, Harefield, Middlesex. Applications are invited for the preregistration post of HOUSE SURGEON to the General Wards at the above Hospital. Vacant immediately.

Applications, with copies of 2 testimonials, to the Medical Director of the Hospital.

HITCHIN. NORTH HERTS HOSPITAL. Applications are invited for the post of RESIDENT HOUSE SURGEON, now vacant. Recognised for the F.R.C.S.

Applications, stating age, nationality, qualifications and experience, together with copies of 3 recent testimonials, to be sent to the Medical Administrator, Lister Hospital, Hitchin, as soon as possible.

HOUNSLOW CHEST CLINIC, 28, Bell-road, Hounslow, MIDDLESEX. NORTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD. REGISTRAR (whole time, non-resident), required at above Clinic. Post vacant now. Clinic has associated beds at Ashford Hospital and West Middlesex Hospital. Good general medical experience essential and special experience in diseases of the chest desirable. Candidates may visit Clinic by direct appointment.

Application forms obtainable from and returnable to the Secretary, Staines Group Hospital Management Committee, Ashford Hospital, London-road, Ashford, Middlesex, by 29th October, 1957.

HUDDERSFIELD ROYAL INFIRMARY. Huddersfield HOSPITAL MANAGEMENT COMMITTEE. Applications are invited from provisionally registered medical practitioners for the post of HOUSE SURGEON to the Princess Royal Maternity Home (57 Beds), to commence duty on 1st December, 1957. The holder of the post, which is recognised for the D.Obst.R.C.O.G., will have access to the abnormal maternity and gynæcological beds at The Royal Infirmary. The Department is under the control of 2 Consultant Obstetricians and Gynæcologists. Salary in accordance with national scale.

Applications, with copies of 3 recent testimonials, to be addressed to—

H. J. JOHNSON, Secretary to the Management Committee.

The Royal Infirmary, Huddersfield.

HUDDERSFIELD ROYAL INFIRMARY. (285 Beds.) HUDDERSFIELD HOSPITAL MANAGEMENT COMMITTEE. HOUSE SURGEON required to commence duty immediately. The post is recognised as a preregistration appointment and for the F.R.C.S. Salary in accordance with National scales.

Applications, together with copies of 3 recent testimonials, to be addressed to the undersigned as soon as possible.

H. J. JOHNSON, Secretary to the Management Committee.

The Royal Infirmary, Huddersfield.

HUDDERSFIELD. ST. LUKE'S HOSPITAL. (235 Beds.) HUDDERSFIELD HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the post of RESIDENT MEDICAL OFFICER (Senior House Officer grade) at the above Hospital, to commence duties immediately. The Hospital caters for chronic sick, children, maternity and acute medical and surgical patients. Salary, in accordance with the terms and conditions of service for hospital medical and dental staffs, £819 10s. p.a.

Applications, together with copies of 3 recent testimonials, to be sent to the undersigned as soon as possible.

H. J. JOHNSON, Secretary to the Management Committee.

The Royal Infirmary, Huddersfield.

ILFORD. KING GEORGE HOSPITAL. There will be a vacancy for a CASUALTY OFFICER at the above Hospital on 8th December, 1957, at a salary of £819 10s. p.a., resident or non-resident. Senior House Officer grade. This post is recognised for the F.R.C.S.

Applications, giving full particulars and accompanied by testimonials, should be sent to the undersigned within 7 days of the appearance of this advertisement.

H. F. HARRIS, Group Secretary,

Ilford and Barking Group Hospital Management Committee.

King George Hospital, Ilford.

KEIGHLEY AND DISTRICT VICTORIA HOSPITAL, KEIGHLEY, YORKS. (General—139 Beds.) 2 RESIDENT HOUSE SURGEONS (either sex).

General surgery and E.N.T., vacant 1st November.

General surgery and orthopædics, vacant 1st November.

Both recognised for F.R.C.S. and approved preregistration appointments, tenable for 6 months in first instance. 4 residents on staff.

Applications, with full particulars as to age, nationality, and qualifications, and copies of 2 testimonials, to Group Secretary, St. John's Hospital, Keighley, Yorks.

IPSWICH AND EAST SUFFOLK HOSPITAL. Anglesea ROAD WING. (356 Beds.) Applications are invited for the post of SENIOR HOUSE SURGEON to the Fracture and Orthopædic Department. The post is graded Senior House Officer and is recognised for the F.R.C.S. examinations. The Department has 2 Consultants, about 60 Beds and a large outpatient attendance ; it offers wide experience.

Applications, stating age, nationality and experience together with copies of recent testimonials to the Hospital Secretary.

IPSWICH AND EAST SUFFOLK HOSPITAL, Heath-road WING, IPSWICH (280 Beds). Applications invited for post of NON-RESIDENT CASUALTY OFFICER (Senior House Officer), vacant immediately. Day-time duties only, offering opportunity of study for higher examinations.

Applications, with full details, to the Hospital Secretary.

ISLEWORTH. WEST MIDDLESEX HOSPITAL. North WEST METROPOLITAN REGIONAL HOSPITAL BOARD. SURGICAL REGISTRAR, Orthopædic and Traumatic Department, whole-time. One year in first instance. Candidates may visit Hospital by appointment with Medical Director.

Application forms obtainable from and returnable to Group Secretary, South West Middlesex Hospital Management Committee, Isleworth, by 29th October.

KETTERING GENERAL HOSPITAL, Kettering. (130 Beds.) KETTERING AND DISTRICT HOSPITAL MANAGEMENT COMMITTEE. Applications are invited from registered medical practitioners for the appointment of SENIOR HOUSE OFFICER in Anæsthetics. Post vacant now. Post recognised for D.A.

Applications, giving details of qualifications and experience, and enclosing copies of 3 recent testimonials, to be sent to the Group Secretary at the above address.

KIRKCALDY GENERAL HOSPITAL. 2 House Officers required to commence duty forthwith. The Hospital has 74 general surgical and orthopædic beds and a busy Casualty and Outpatient Department. The posts qualify for preregistration. Salary in accordance with National scales.

Apply, in writing, to the Medical Superintendent, East Fife Hospitals Board of Management, 243A, High-street, Kirkcaldy.

LEAMINGTON SPA. WARNEFORD GENERAL HOS-PITAL. (197 Beds.) HOUSE PHYSICIAN. Vacancy suitable for fully qualified or preregistration applicant. Post vacant 15th November, 1957.

Applications, with copies of 2 recent testimonials, to be sent to Hospital Secretary.

LEAMINGTON SPA. WARNEFORD GENERAL HOS-PITAL. (197 Beds.) CASUALTY OFFICER (Senior House Officer), Male or Female, resident or non-resident. Post vacant 12th November, 1957, and suitable for one reading for higher qualifications being recognised for F.R.C.S., affording contact with all Specialist Units in the Hospital.

Applications, with names and addresses of 3 referees, to Hospital Secretary.

LEEDS REGIONAL HOSPITAL BOARD. Registrar vacancies.

Plastic Surgery

St. James's Hospital, Leeds (non-resident). Special Plastic and Maxillo-Facial Unit. (72 Beds.)

Psychiatry

(i) Menston Hospital, near Leeds (2500 Beds).

(ii) Oulton Hall Hospital, near Wakefield, and Affiliated Mental Deficiency Colonies (approximately 400 Beds). Non-resident.

(iii) Stanley Royd Hospital, Wakefield (2000 Beds). Recognised for D.P.M.

(iv) Storthes Hall Hospital, Kirkburton, Huddersfield (2750 Beds).

If desired, facilities for attendance at the Leeds University will be provided, if the successful candidates are studying for the D.P.M.

Applications, stating age, qualifications and details of present and previous appointments with dates, together with the names and addresses of 3 referees, to the Secretary, Joint Registrars Committee, Park-parade, Harrogate, by 30th October, 1957.

LEEDS REGIONAL HOSPITAL BOARD. Registrar vacancies.

General Surgery

Clayton Hospital, Wakefield (75 general surgical beds). Duties are those of Resident Surgical Officer, married quarters available. Recognised for F.R.C.S., may include some duties in the Casualty Department.

Obstetrics and Gynæcology

St. Luke's Hospital, Bradford (118 obstetric and 105 gynæcological beds). New post awaiting recognition for M.R.C.O.G. Resident.

Applications, stating age, qualifications, and details of present and previous appointments with dates, together with the names and addresses of 3 referees, to the Secretary, Joint Registrars Committee, Park-parade, Harrogate, by 23rd October, 1957.

LEEDS. THE UNITED LEEDS HOSPITALS. Applications are invited for the post of ASSISTANT RESIDENT MEDICAL OFFICER at the General Infirmary at Leeds. The post is of Registrar status and will be tenable for 1 year from 1st January, 1958, in the first instance.

Applications, stating age, qualifications, previous posts with dates, together with the names of 3 referees, should be forwarded not later than 30th October, 1957, to the Sub-Dean, School of Medicine, Leeds, 2.

LEEDS. THE UNITED LEEDS HOSPITALS. Senior HOUSE OFFICER in General Medicine required for duties at the General Infirmary at Leeds and the pre-convalescent annexe. Residential accommodation available for single person, house available for married officer, at reasonable rental. Appointment tenable for 1 year. Post vacant 1st November, 1957.

Applications, stating age, qualifications, and experience and 3 names for reference, to be sent to the Secretary to the Board, The General Infirmary, Leeds, 1, by not later than 30th October, 1957.

LLWYNYPIA HOSPITAL, Llwynypia, Rhondda. (213 Beds including acute medical and chronic sick beds.) HOUSE OFFICER (medical). Person appointed will also undertake duties at the Group Infectious Diseases Hospital when required.

Applications, stating age, qualifications, and experience, together with copies of 2 recent testimonials, to be sent to the Group Secretary, Pontypridd and Rhondda Hospital Management Committee, Courthouse-street, Pontypridd.

LANCASTER MOOR HOSPITAL, Lancaster. Regional Mental Hospital. Applications are invited for the post of RESIDENT JUNIOR HOSPITAL MEDICAL OFFICER (Male or Female). Unfurnished house available; furnished quarters for married couple (without children) or single person. Hospital recognised for D.P.M. and facilities granted for attending neighbouring universities. All modern methods of investigation and treatment carried out. Hospital serving N. Lancashire and Lake District. Post for initial period of 4 years, but renewable if services satisfactory.

Apply Medical Superintendent.

LEICESTER ROYAL INFIRMARY. Applications are invited for the post of SENIOR HOUSE OFFICER/INTERN in Surgical Department, now vacant. Recognised for F.R.C.S.

Applications, stating age, qualifications and experience, together with copies of recent testimonials, to Group Secretary, No. 1 Hospital Management Committee, The Leicester Royal Infirmary, immediately.

LLANELLY HOSPITAL, Llanelly. (164 Beds.) Glantawe HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the appointment of SENIOR HOUSE OFFICER in the Casualty Department of the above Hospital.

Full particulars, stating age, experience and qualifications, together with copies of 2 recent testimonials should be forwarded to the Hospital Secretary. T. E. JONES, Group Secretary.

LLANELLY HOSPITAL, Llanelly. (164 Beds.) Glantawe HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the post of JUNIOR HOSPITAL MEDICAL OFFICER in Anæsthetics at above Hospital. The Hospital is recognised for the D.A. examination. The successful candidate will be granted facilities to attend monthly anæsthetic lectures and discussions which are held at the Cardiff Royal Infirmary.

Applications, stating age, experience and qualifications, together with the names of 2 referees, should be sent to the Secretary of the Hospital. T. E. JONES, Group Secretary.

MAIDSTONE. PRESTON HALL HOSPITAL, British LEGION VILLAGE, MAIDSTONE, KENT. Applications are invited for the post of JUNIOR HOSPITAL MEDICAL OFFICER at the above Hospital, which contains 330 Beds for treatment of pulmonary tuberculosis and other chest diseases, and includes a major Thoracic Surgical Unit. Candidates should have had experience in general medicine and in the treatment of chest diseases in adults. Salary £852 10s.–£55–£1182 10s. p.a. National scale and conditions. Married accommodation available shortly.

Applications, stating age, qualifications and experience with relevant dates, together with names and addresses of 2 referees, to be sent to the Group Secretary by 25th October, 1957.

MANCHESTER REGIONAL HOSPITAL BOARD. SALFORD HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the post of RESIDENT MEDICAL OFFICER (Registrar grade) at Salford Royal Hospital.

Applications, together with names and addresses of 2 referees, to be sent to Group Secretary, Salford Royal Hospital, Salford, 3, before 26th October, 1957.

MANCHESTER REGIONAL HOSPITAL BOARD AND UNITED MANCHESTER HOSPITALS. SENIOR REGISTRAR IN SURGERY in the Salford Group of Hospitals, mainly at Salford Royal Hospital. The post is included in the regional rotation scheme and it is expected that the person appointed will later transfer to the Manchester Royal Infirmary.

Application forms from the Senior Administrative Medical Officer of the Board, Cheetwood-road, Manchester, 8, to be returned by 4th November, 1957.

MANCHESTER REGIONAL HOSPITAL BOARD. BOL-TON DISTRICT GENERAL HOSPITAL. (607 Beds.) RESIDENT REGISTRAR in General Surgery (Resident Surgical Officer). Recognised for F.R.C.S. The post is the senior resident surgical appointment and offers excellent practical experience.

Applications, stating age, nationality, qualifications, experience, and the names of 2 referees, should be sent immediately to Group Secretary, Bolton and District Hospital Management Committee, The Royal Infirmary, Bolton.

MANCHESTER REGIONAL HOSPITAL BOARD. North AND MID-CHESHIRE HOSPITAL MANAGEMENT COMMITTEE. REGISTRAR (chest diseases) required to carry out duties arranged by the Consultant Chest Physician at the Altrincham, Northwich, Crewe Chest Clinics and Hefferstone Grange Sanatorium, to commence November, 1957. Accommodation might be arranged, if necessary.

Applications, together with 2 recent testimonials, should be sent to the Group Secretary, North and Mid-Cheshire Hospital Management Committee, The Hospital, Sinderland-road, Altrincham, Cheshire.

MANCHESTER REGIONAL HOSPITAL BOARD invites applications for the post of MEDICAL REGISTRAR at the Devonshire Royal Hospital, Buxton, vacant on 1st December, 1957. The main duties will be in the Department of Physical Medicine with some duties in the Hospital. The post offers excellent opportunities in research. Previous physical medicine experience desirable. Interest in experimental work an advantage. Unfurnished accommodation on rental may be made available to male married applicant.

Applications, together with the names of 2 referees, to be forwarded to the Group Secretary, Stockport and Buxton Hospital Management Committee, 59B, Shaw-heath, Stockport.

MANCHESTER, 20. CHRISTIE HOSPITAL AND HOLT RADIUM INSTITUTE, SOUTH MANCHESTER HOSPITAL MANAGEMENT COMMITTEE. Applications are invited from registered practitioners for the post of ASSISTANT RESIDENT SURGICAL OFFICER (Senior House Officer grade). The post provides experience in the treatment of tumours and good opportunity for study.

Applications, with full details, including the names of 2 referees to be forwarded to the Group Secretary, Withington Hospital, Manchester, 20, immediately.

MANCHESTER NORTHERN HOSPITAL. Applications are invited for the resident post of SENIOR HOUSE OFFICER in Gynæcology. Recognised for M.R.C.O.G. Vacant 2nd December, 1957.

Applications, with names of 2 referees, by 28th October, 1957, to Group Secretary, North Manchester Hospital Management Committee, Crumpsall Hospital, Manchester, 8.

MANCHESTER. WEST MANCHESTER HOSPITAL MANAGEMENT COMMITTEE. PARK HOSPITAL, DAVYHULME. (General Hospital—433 Beds.) SENIOR HOUSE OFFICER (general surgery) required. Post vacant end November.

Application forms from Secretary.

MARKET DRAYTON, SHROPSHIRE. CHESHIRE JOINT SANATORIUM. SENIOR HOUSE OFFICER required for inpatient and outpatient duties with Thoracic Surgical Unit dealing with tuberculous and non-tuberculous cases for a population of approximately 500,000.

Applications, with copy testimonials, to Group Secretary, Hospital Management Committee, Princes-road, Stoke-on-Trent, as soon as possible.

MORECAMBE. QUEEN VICTORIA HOSPITAL. RESIDENT SENIOR HOUSE OFFICER (surgical). The post is normally tenable 1 year and the successful applicant will be attached to the specialist Surgical Unit. Post vacant now.

Applications, with names of 2 referees, to be addressed to the Group Secretary, Royal Lancaster Infirmary, Lancaster.

MITCHAM. WILSON HOSPITAL, Cranmer-road, MITCHAM, SURREY. RESIDENT HOUSE PHYSICIAN (not preregistration). Vacant 25th November.

Applications, stating age, qualifications, etc., with the names and addresses of 2 referees, to the Secretary at above address.

MITCHAM. WILSON HOSPITAL, Cranmer-road, MITCHAM, SURREY. RESIDENT SENIOR HOUSE SURGEON (not recognised for F.R.C.S.). Vacant 1st December. This post in small but busy General Hospital provides good and varied experience in diagnosis, treatment and operative procedure.

Applications, stating age, qualifications, experience and names of referees, to the Group Secretary, St. Helier Hospital, Carshalton, Surrey.

NEWCASTLE REGIONAL HOSPITAL BOARD. REGISTRAR ANÆSTHETIST, whole-time, for Sunderland group of hospitals. Post recognised for F.F.A.R.C.S. Single accommodation available.

Applications, with names and addresses of 3 referees, to Senior Administrative Medical Officer, Regional Hospital Board, Benfield-road, Newcastle upon Tyne, 6, within 14 days.

NEWCASTLE REGIONAL HOSPITAL BOARD. REGISTRAR THORACIC SURGEON, whole-time, resident, at Regional Thoracic Centre (150 Beds), Shotley Bridge General Hospital (work almost entirely non-tuberculosis (cardiovascular, œsophageal and pulmonary)) and at associated sanatoria. Applicants must have good experience in general surgery and have a higher qualification or its equivalent. Appointment intended either for trainee in thoracic surgery or for general surgeon seeking special experience. Single accommodation available.

Applications, with names and addresses of 3 referees, to Senior Administrative Medical Officer, Regional Hospital Board, Benfield-road, Newcastle upon Tyne, 6, within 14 days.

NEWCASTLE REGIONAL HOSPITAL BOARD. 2 REGISTRAR PÆDIATRICIANS to work in the Newcastle upon Tyne group of hospitals and United Newcastle Hospitals. Posts offer experience in various branches of pædiatrics and rotation may include Newcastle General Hospital, Hospital for Sick Children, Royal Victoria Infirmary and Princess Mary Maternity Hospital. 1 candidate will commence duties in Children's Department, Newcastle General Hospital. Duties connected with teaching, &c.

Applications, with names and addresses of 3 referees, to Senior Administrative Medical Officer, Regional Hospital Board, Benfield-road, Newcastle upon Tyne, 6, within 14 days.

NEWCASTLE UPON TYNE. WALKER GATE HOSPITAL. (309 Beds.) NEWCASTLE UPON TYNE HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the post of SENIOR HOUSE OFFICER to the 90-bed Medical Unit of this Hospital. The work is mainly pædiatrics and infectious diseases and offers excellent clinical facilities for anyone wishing to gain pædiatric experience.

Applications, together with the names of 3 referees, to be forwarded immediately to the Hospital Secretary, Walker Gate Hospital, Newcastle, 6.

NORWICH. NORFOLK AND NORWICH HOSPITAL. Locum ORTHOPÆDIC REGISTRAR required immediately until the 23rd December, 1957. Resident or non-resident. Salary £19 5s. per week in accordance with terms and conditions of service of hospital medical staff. Membership of a Medical Defence Society is a condition of appointment.

Applications, stating age, qualifications and experience, together with names of 2 referees, to Group Secretary, Hospital Management Committee, St. Stephen's-road, Norwich.

OXFORD. UNITED OXFORD HOSPITALS. Applications invited for post of NON-RESIDENT REGISTRAR in the Tuberculous Meningitis Unit at the Osler Hospital, Headington, Oxford, commencing on 1st November, 1957. The post will be for 1 year in the first instance, but eligible for extension to a second year.

Applications, on forms obtainable from the Administrator, Radcliffe Infirmary, Oxford, should be received as soon as possible.

NOTTINGHAM. CITY HOSPITAL. (611 Beds.) Applications are invited for the post of RESIDENT PATHOLOGIST (Senior House Officer). Previous experience an advantage. Post vacant 14th November, 1957.

Applications, stating age, nationality, qualifications and experience, together with copies of not more than 3 testimonials, to be sent to the Hospital Secretary, City Hospital, Hucknall-road, Nottingham.

NOTTINGHAM. CITY HOSPITAL. (611 Beds.) Applications are invited for the post of HOUSE SURGEON, vacant 4th November, 1957. Recognised for pre-registration purposes.

Applications, stating age, nationality, qualifications and experience, together with copies of not more than 3 testimonials, to be sent to the Hospital Secretary, City Hospital, Hucknall-road, Nottingham.

NOTTINGHAM GENERAL HOSPITAL. A Senior House OFFICER (Orthopædic and Fracture) required as soon as possible. Post offers exceptional experience in traumatic surgery. Locum considered for any period.

Applications, stating age, qualifications and experience, together with copies of testimonials, to be sent to Group Secretary.

OXFORD REGIONAL HOSPITAL BOARD. Orthopædic REGISTRAR (whole-time) to the Nuffield Orthopædic Centre (Wingfield Morris Hospital), Oxford. Available 1st November. Single accommodation available if required. Appointment for 1 year in first instance, renewable for a second year.

Applications on forms obtainable from Secretary, Registrar Committee, 43, Banbury-road, Oxford, should reach him by 24th October, 1957.

OXFORD REGIONAL HOSPITAL BOARD. United OXFORD HOSPITALS. SENIOR REGISTRAR IN PATHOLOGY to Stoke Mandeville Hospital. This is a central clinical laboratory serving Stoke Mandeville and the Aylesbury Hospitals and acting as parent to High Wycombe and Amersham laboratories. It is closely connected with research projects being undertaken at Stoke Mandeville Hospital. Under an exchange scheme the second half of the appointment may be undertaken in the Pathology Department of the United Oxford Hospitals. Appointment for 1 year in the first instance, eligible for extension up to 4 years. Applicants may visit Stoke Mandeville Hospital by arrangement with the Pathologist.

Applications, on forms obtainable from the Secretary, Joint Committee for Senior Registrars (from whom further particulars may be obtained), 43, Banbury-road, Oxford, should be received by him by 31st October, 1957.

PLYMOUTH. MOUNT GOLD ORTHOPÆDIC HOSPITAL. Applications are invited for the post of SENIOR HOUSE OFFICER for the Orthopædic and Fracture Service centring on Mount Gold Orthopædic and associated hospitals. Post recognised by R.C.S.

Applications, stating age, qualifications with dates, &c., and with copies of 2 recent testimonials, to be forwarded to the Secretary, Mount Gold Hospital, Plymouth, within 14 days of this advertisement appearing.

PLYMOUTH. SOUTH DEVON AND EAST CORNWALL HOSPITAL.

SENIOR HOUSE OFFICER, vacant 1st December, 1957. Devonport Hospital. Recognised for the F.R.C.S.

Applications to the Group Secretary, 7, Nelson-gardens, Devonport.

HOUSE SURGEON (preregistration post), vacant 2nd November, 1957. Devonport Hospital. Recognised for the F.R.C.S.

Applications to the Group Secretary, 7, Nelson-gardens, Devonport.

HOUSE PHYSICIAN (preregistration post), vacant 1st January, 1958.

Applications to the Group Secretary, Greenbank Road Hospital, Plymouth.

HOUSE SURGEONS (preregistration posts), vacancies 9th December, 1957, 1st and 4th January, 1958. Recognised for the F.R.C.S.

Applications to the Group Secretary, Greenbank Road Hospital, Plymouth.

PÆDIATRIC HOUSE PHYSICIAN (preregistration post), vacant 1st January, 1958. Recognised for the D.C.H.

Applications to the Group Secretary, Freedom Fields Hospital, Plymouth.

In all cases send names of 3 referees.

PORTSMOUTH GROUP HOSPITAL MANAGEMENT COMMITTEE.

(i) **Infectious Diseases Hospital**

SENIOR HOUSE OFFICER required with duties also on the Tuberculosis Wards and the Poliomyelitis Diagnostic and Respiratory Centre. Vacant now.

(ii) **Royal Portsmouth Hospital**

Orthopædic Department (104 Beds)

HOUSE OFFICER (preregistration), vacant 1st November, 1957.

Applications, stating age, experience and qualifications, together with the names of 2 referees, should be forwarded as soon as possible to E. H. HURST.

St. Mary's Hospital, Milton-road, Portsmouth.

RICHMOND, SURREY. CASSEL HOSPITAL FOR FUNCTIONAL NERVOUS DISORDERS. SOUTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD. Applications are invited for the Part time (5/11ths) post of JUNIOR HOSPITAL MEDICAL OFFICER. Preference given to applicants having experience or interest in psychotherapy and must have special interest in psychoanalysis. Candidates may visit the Hospital by appointment.

Application forms may be obtained from the undersigned and should be returned to the Secretary within 14 days of the appearance of this advertisement.

D. MALLION, Secretary,
Cassel Hospital Management Committee,
Ham Common, Richmond.

ROMFORD, ESSEX. VICTORIA HOSPITAL. (99 Beds.) RESIDENT HOUSE PHYSICIAN (Male) required immediately. Not preregistration appointment.

Applications should be forwarded to the Secretary, Romford Group Hospital Management Committee, Oldchurch Hospital, Romford.

ROMFORD, ESSEX. OLDCHURCH HOSPITAL. (722 Beds.) RESIDENT HOUSE SURGEONS (2) required from 1st December, 1957, in the General Surgical Unit. Recognised for F.R.C.S. Open to either preregistration applicants or to fully qualified practitioners. This very active unit of a total of approximately 180 Beds affords ample opportunities for candidates to obtain first-class tuition and experience. The candidates appointed will be attached to a unit of approximately 60 Beds.

Applications should be forwarded to the Group Secretary, Romford Group Hospital Management Committee, Oldchurch Hospital, Romford.

READING. BATTLE HOSPITAL. (391 Beds.) Applications are invited from registered medical practitioners for the post of RESIDENT JUNIOR HOUSE SURGEON in the Accident and Orthopædic Department. Post vacant 1st November, 1957. F.R.C.S. recognised. Also casualty duties.

Apply, stating age, qualifications with dates, nationality, present post, with 1 copy of recent testimonial, to Hospital Secretary.

SALFORD ROYAL HOSPITAL. Salford Hospital Management Committee. SENIOR HOUSE OFFICER in Pathology required. Resident.

Applications, with names and addresses of 2 referees, to be addressed to the Secretary, Salford Royal Hospital, Chapel-street, Salford, 3, Lancs.

SCOTLAND. EASTERN REGIONAL HOSPITAL BOARD. RADIODIAGNOSIS. DUNDEE TEACHING HOSPITALS. Applications are invited for an appointment as SENIOR REGISTRAR in Radiodiagnosis at Dundee Royal Infirmary (534 Beds), the main general teaching Hospital associated with the University of St. Andrews. Salary and conditions of service in accordance with National Agreement.

Forms of application and further particulars from the Secretary to the Board, 430, Blackness-road, Dundee, with whom applications must be lodged not later than 2nd November, 1957.

SCOTLAND. EASTERN REGIONAL HOSPITAL BOARD. DUNDEE AREA. Thoracic (and cardiac) surgery. Applications are invited for the appointment of REGISTRAR in Surgery for duty in the Regional Thoracic Surgical Centre at Ashludie Hospital, Monifieth, by Dundee (222 Beds—60 for thoracic surgery), and in the Cardiovascular Department of the Professorial Surgical Unit at Dundee Royal Infirmary (the principal general teaching hospital associated with the University of St. Andrews—534 Beds). Previous experience in thoracic surgery and in general chest medicine an advantage. Salary and conditions of service in accordance with national agreement.

Further particulars and forms of application from the Secretary to the Board, 430, Blackness-road, Dundee, with whom applications must be lodged not later than 26th October, 1957.

SCOTLAND. SOUTH-EASTERN REGIONAL HOSPITAL BOARD. REGISTRAR to the Royal Edinburgh Hospital for Mental and Nervous Disorders, from 16th January, 1958. During tenure of post opportunities for study and interchange of duty and training at other centres in the Region may be available under joint training scheme of South-Eastern Regional Hospital Board and Department of Psychological Medicine of the University of Edinburgh. Single accommodation available. The Hospital may be visited by arrangement with the Physician Superintendent.

Apply, giving particulars of age, qualifications and previous experience and the names of 2 referees, to the Secretary, 11, Drumsheugh-gardens, Edinburgh, within 14 days.

SCOTLAND. SOUTH-EASTERN REGIONAL HOSPITAL BOARD. REGISTRAR in Surgery at the Royal Infirmary of Edinburgh, vacant on 21st December, 1957.

Apply, giving particulars of age, qualifications and previous experience, together with the names of 2 referees, to the Secretary, 11, Drumsheugh-gardens, Edinburgh, 3, by 9th November, 1957.

SCOTLAND. SOUTH-EASTERN REGIONAL HOSPITAL BOARD. SENIOR REGISTRAR in Radiotherapy at the Royal Infirmary and Western General Hospital, Edinburgh.

Apply, giving particulars of age, qualifications and previous experience, together with the names of 3 referees, to the Secretary, South-Eastern Regional Hospital Board, 11, Drumsheugh-gardens, Edinburgh, 3, by 9th November, 1957.

SCOTLAND. SOUTH-EASTERN REGIONAL HOSPITAL BOARD. Locum Tenens REGISTRAR IN PSYCHIATRY based on Jordanburn Nerve Hospital, Edinburgh.

Apply, giving qualifications and names of 2 referees, to Secretary, 11, Drumsheugh-gardens, Edinburgh, 3.

SCOTLAND. SOUTH-EASTERN REGIONAL HOSPITAL BOARD. Locum Tenens REGISTRAR IN SURGERY for duty in the Dunfermline and West Fife Hospital for 2 months from 6th December, 1957.

Apply, giving qualifications and names of 2 referees, to the Secretary, 11, Drumsheugh-gardens, Edinburgh, 3.

SCOTLAND. WESTERN REGIONAL HOSPITAL BOARD. Applications are invited for the following appointments, which will be for 1 year in the first instance :—

REGISTRAR in E.N.T. Surgery for duties on a rotational basis at the Ear, Nose and Throat Hospital, and the Western Infirmary, Glasgow.

REGISTRAR in E.N.T. Surgery based at the Royal Infirmary, Glasgow, for duties at Law Hospital, Carluke.

REGISTRAR in E.N.T. Surgery based at Stobhill General Hospital, Glasgow.

REGISTRAR in Pathology based at the Dumfries and Galloway Royal Infirmary, Dumfries.

REGISTRAR in Surgery based at Law Hospital, Carluke.

REGISTRAR in Psychiatry for duties at Bellsdyke Mental Hospital, Larbert, and at H.M. Institution, Polmont.

Applications (12 copies), stating date of birth, qualifications, experience, present appointment, and the names of 3 referees, to reach the Secretary, Western Regional Hospital Board, 64, West Regent-street, Glasgow, C.2, by 2nd November, 1957.

SHEFFIELD. THE UNITED SHEFFIELD HOSPITALS. ROYAL INFIRMARY. Applications invited for the non-resident or resident post of CASUALTY AND ORTHOPÆDIC REGISTRAR in the Orthopædic and Accident Department at the above Hospital. Post vacant 4th December. Post recognised for Casualty requirements for the final F.R.C.S.

Applications, stating age, qualification and experience, with the names of 3 referees, should be sent not later than 2nd November, 1957, to the Chief Administrative Officer, The United Sheffield Hospitals, West-street, Sheffield, 1.

SHOREHAM-BY-SEA. SOUTHLANDS HOSPITAL. WORTHING GROUP HOSPITAL MANAGEMENT COMMITTEE. HOUSE SURGEON, post recognised by R.C.S. for Fellowship; entails duties in general surgery and orthopædics. Vacant 21st November.

Applications to Secretary, Southlands Hospital, Shoreham-by-Sea, Sussex. A. V. OAKTON, Group Secretary.

SHREWSBURY. ROYAL SALOP INFIRMARY/COPTHORNE HOSPITAL. (500 Beds.) HOUSE PHYSICIAN preregistration candidates eligible. Vacant 24th October, 1957.

Applications with copy testimonials to Group Secretary, Shrewsbury Hospital Group, Royal Salop Infirmary, Shrewsbury.

SHREWSBURY. ROYAL SALOP INFIRMARY/COPTHORNE HOSPITAL. (500 Beds.) HOUSE SURGEON. Vacant 1st November, 1957. Preregistration candidates eligible. Recognised for the F.R.C.S.

Applications, with copy testimonials, to Group Secretary, Shrewsbury Hospital Group, Royal Salop Infirmary, Shrewsbury.

SIDCUP, KENT. QUEEN MARY'S HOSPITAL. Senior HOUSE OFFICER (casualty and orthopædic), required from 15th November, 1957. The successful applicant will serve 3 months in the Orthopædic Department and 3 months as Casualty Officer. The post is recognised under the Fellowship regulations as a period of 6 months casualty training.

Applications, stating age, qualifications and experience, together with names and addresses of 2 referees, should be sent to the Secretary.

SLOUGH, BUCKINGHAMSHIRE. UPTON HOSPITAL. SENIOR HOUSE OFFICER (casualty) required, working with Casualty Registrar in busy Casualty Department. Post recognised for F.R.C.S. Experience given in plastic and orthopædic cases.

Applications, with names of 2 referees, to Secretary.

SLOUGH, BUCKINGHAMSHIRE. UPTON HOSPITAL. RESIDENT LOCUM ANÆSTHETIC REGISTRAR required 1st–14th November.

Applications, with names of 2 referees, to Secretary.

SLOUGH, BUCKINGHAMSHIRE. UPTON HOSPITAL. MEDICAL REGISTRAR required. Resident or non-resident (resident when nights on duty).

Application forms from and returnable to Secretary, Windsor Hospital Management Committee, Alma-road, Windsor, by 2nd November.

STOCKTON-ON-TEES. SEDGEFIELD GENERAL HOSPITAL, SEDGEFIELD. SENIOR HOUSE OFFICER PHYSICIAN and Preregistration HOUSE PHYSICIAN urgently required. Full Consultant staff employed; both posts offer excellent opportunity for further study, a good resident's library is provided; married accommodation available.

Applications immediately to the Group Secretary, Sedgefield Hospital Management Committee, at the above address.

STOCKPORT AND BUXTON HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the following post, which is approved for preregistration purposes.

Stockport Infirmary (163 Beds)

HOUSE OFFICER (general surgery and gynæcology). Recognised for the F.R.C.S. Vacant now.

Applications, with copies of 2 testimonials, to the Group Secretary, 59B, Shaw-heath, Stockport.

STOCKPORT. STEPPING HILL HOSPITAL. (529 Beds.) STOCKPORT AND BUXTON HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the post of SENIOR HOUSE OFFICER (pædiatrics). The post, which may be either resident or non-resident, becomes vacant on 1st December, 1957.

Applications, stating age, qualifications and experience, together with copies of 2 testimonials, to be addressed to the Secretary, Stockport and Buxton Hospital Management Committee, 59B, Shaw-heath, Stockport.

STOCKPORT. CHERRY TREE HOSPITAL. (Isolation—96 Beds.) Applications are invited for the post of SENIOR HOUSE OFFICER, vacant now. This Hospital is associated with Manchester University for the study of Infectious Diseases, and the successful candidate will have ample opportunity for study.

Applications, with full particulars and copies of 2 recent testimonials, to the Secretary, Stockport and Buxton Hospital Management Committee, 59B, Shaw-heath, Stockport, Cheshire.

STOKE-ON-TRENT. CITY GENERAL HOSPITAL. (815 Beds.) HOUSE OFFICER (general surgery) required, vacant now. Preregistration post. Hospital recognised for F.R.C.S.

Detailed applications, with copy testimonials, to Group Secretary, Hospital Management Committee, Princes-road, Stoke-on-Trent.

STOKE-ON-TRENT. NORTH STAFFORDSHIRE ROYAL INFIRMARY. (455 Beds.) SENIOR HOUSE OFFICER (Ophthalmology) required. Recognised F.R.C.S. and D.O.

Applications to Group Secretary, Hospital Management Committee, Princes-road, Stoke-on-Trent.

SWANSEA HOSPITAL (413 Beds) Swansea. Glantawe HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the post of SENIOR HOUSE OFFICER in the Gynæcological Department at the above Hospital.

Applications, with full particulars, should be addressed to the Hospital Secretary. T. E. JONES, Group Secretary.

SOUTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD. PSYCHIATRIC REGISTRARS training scheme. Applications are invited for the appointment of REGISTRAR for 6 months' periods at the Hospitals of St. Ebba's, Horton, Long Grove and The Manor in succession. Wide experience is available in all forms of psychosis, in neurosis and in mental deficiency under modern methods of treatment. Special experience may be gained in the Mott Clinic for General Paralysis, St. Ebba's Juvenile Unit and in Mapother House, Long Grove, for acute psychosis; also in the observation wards and outpatient departments. The appointment will be tenable from January, 1958. Salary, &c., in accordance with the agreed terms and conditions of service of hospital medical staff. For residents appropriate charges are made for full residential amenities. Candidates may visit the hospitals by appointment with the Physicians Superintendent.

Application forms may be obtained from the Group Secretary, St. Ebba's and Belmont Group Hospital Management Committee, Group Office, Belmont Hospital, Brighton-road, Sutton, Surrey, and completed forms (5 copies) should be returned to him within 2 weeks of the appearance of this advertisement.

SOUTHAMPTON. ROYAL SOUTH HANTS HOSPITAL. (274 Beds.) RESIDENT HOUSE PHYSICIAN required. Preregistration candidates eligible.

Applications, with copies of testimonials, should be forwarded to Group Secretary, Southampton Group Hospital Management Committee, Bullar Street, Southampton, as soon as possible.

SOUTHAMPTON. ROYAL SOUTH HANTS HOSPITAL. (274 Beds. Recognised for F.R.C.S.) ORTHOPÆDIC HOUSE SURGEON (post recognised for Preregistration Service and tenable for 6 months). The Hospital is the centre to which all trauma from a large industrial town and port is directed thus providing excellent experience in the treatment of traumatic conditions; patients with orthopædic conditions are also drawn from a wide area.

Applications, with copies of testimonials, should be sent as soon as possible to the Group Secretary, Southampton Group Hospital Management Committee, Bullar-street, Southampton.

SOUTHAMPTON. ROYAL SOUTH HANTS HOSPITAL. (274 Beds.) RESIDENT HOUSE SURGEON required. Preregistration candidates eligible.

Applications, with copies of recent testimonials, should be forwarded to Group Secretary, Southampton Group Hospital Management Committee, Bullar-street, Southampton.

SOUTHAMPTON GENERAL HOSPITAL. (474 Beds.) RESIDENT HOUSE PHYSICIAN required mid-November. Preregistration candidates eligible.

Applications, with copies of testimonials, should be forwarded as soon as possible to the Group Secretary, Southampton Group Hospital Management Committee, Bullar-street, Southampton.

SUTTON, SURREY. BANSTEAD HOSPITAL. (2400 Beds.) Applications are invited for the post of PSYCHIATRIC REGISTRAR at the above Hospital, which offers full facilities for training in psychiatry, including the special study of neuroses and child guidance. Courses in psychology are arranged for the D.P.M. Residence is optional, at present accommodation is only available for a single person, but a flat may soon become available.

Candidates should apply to the Secretary, Banstead Hospital, Sutton, Surrey, for forms of application, which should be returned duly completed, within 14 days of the appearance of this advertisement. Candidates should visit the Hospital by arrangement with the Physician-Superintendent.

SUTTON AND CHEAM HOSPITAL, Cotswold-road, SUTTON, SURREY. RESIDENT SENIOR HOUSE OFFICER (Casualty Officer). Post recognised for F.R.C.S. Vacant 1st November.

Applications, stating age, qualifications and experience, with copies of recent testimonials and the names of 2 referees, to the Group Secretary, St. Helier Hospital, Carshalton, Surrey.

TAUNTON AND SOMERSET HOSPITAL. Senior House OFFICER (general medicine) required end of October. Post also gives opportunity of work in Area Pathological Laboratory if desired.

Applications, stating age, nationality and qualifications, together with the names of 2 referees, should be forwarded to the Group Secretary, Taunton Hospital Management Committee, Taunton and Somerset Hospital, Musgrove Park Branch, Taunton, Somerset.

TEES-SIDE HOSPITAL MANAGEMENT COMMITTEE. SENIOR HOUSE OFFICER required for Neuro-Surgical Department of 24 Beds opening on the 1st November, 1957. Post offers wide experience in Neurology. No previous experience necessary.

Applications, with names of 2 referees, to Hospital Secretary, Hemlington Hospital, Middlesbrough.

TREDEGAR GENERAL HOSPITAL, Monmouthshire. RHYMNEY AND SIRHOWY VALLEYS HOSPITAL MANAGEMENT COMMITTEE. RESIDENT SURGICAL OFFICER (Junior Hospital Medical Officer grade) required for Surgical Unit at above Hospital. Duties are those of Assistant to General Surgeon; staff includes also House Surgeon. Commodious family flat.

Apply, with full particulars and stating names of 2 referees, to Secretary.

WINCHESTER. ROYAL HAMPSHIRE COUNTY HOSPITAL. (315 Beds.) HOUSE PHYSICIAN (preregistration) vacant immediately.

Applications, with copy of 2 testimonials, to the Group Secretary.

WINCHESTER. ROYAL HAMPSHIRE COUNTY HOSPITAL (315 Beds). SENIOR HOUSE OFFICER (orthopædics) required. Post recognised F.R.C.S. Wide experience available under Area Orthopædic team. Appointment for 6 months in first instance. Vacant 11th November.

Applications, with copies of 2 testimonials, to the Group Secretary.

TAPLOW, near MAIDENHEAD. CANADIAN RED CROSS MEMORIAL HOSPITAL. HOUSE PHYSICIAN required for post vacant 24th November. Preregistration post.

Applications, stating age, experience, and qualifications with dates, with copies of 2 testimonials, to Secretary.

TUNBRIDGE WELLS (near). PEMBURY HOSPITAL, PEMBURY. Applications are invited for the appointment of SENIOR ORTHOPÆDIC HOUSE SURGEON AND CASUALTY OFFICER (Senior House Officer grade) to begin duties as soon as possible. Recognised F.R.C.S. (Eng.) and tenable for 1 year. Work includes treatment of long and short stay cases and traumatic surgery with large outpatient and fracture clinics under 2 Consultants.

Apply, stating age, qualifications, and experience, together with 3 testimonials, to Group Secretary, Sherwood Park, Pembury-road, Tunbridge Wells.

WAKEFIELD. STANLEY ROYD HOSPITAL. Applications invited for post of JUNIOR HOSPITAL MEDICAL OFFICER or SENIOR HOUSE OFFICER in Psychiatry. Accommodation available for single person and may be available for a married person.

Address applications, giving full personal particulars, details of training, experience, and 2 names and addresses for reference, to W. BOWRING, Group Secretary.

Pinderfields General Hospital, Wakefield.

WAKEFIELD. STANLEY ROYD HOSPITAL. Locum Tenens JUNIOR HOSPITAL MEDICAL OFFICER in Psychiatry required. Salary £19 5s. per week. Accommodation for single person at charge of £3 5s. 6d. per week.

Address written applications to W. BOWRING, Group Secretary. Pinderfields General Hospital, Wakefield.

WARRINGTON INFIRMARY. Applications are invited from Males and Females for the post of RESIDENT CASUALTY OFFICER (graded as Junior Hospital Medical Officer) at the above Hospital. The post becomes vacant on 1st November, 1957, and is recognised for the F.R.C.S. Scale of salary £852 10s.–£55–£1182 10s., less a deduction of £170 for the residential emoluments. A whole-time Senior Hospital Medical Officer is in charge of the Department.

Applications, stating age, experience and qualifications, should be forwarded to—

HENRY L. BOOT, Group Secretary,
Warrington and District Hospital Management Committee.
c/o General Hospital, Warrington, Lancs.

WATFORD, HERTFORDSHIRE. PEACE MEMORIAL HOSPITAL. CASUALTY OFFICER (Senior House Officer) Modern Department employing 3 full-time Casualty Officers. Post recognised for F.R.C.S. Resident or non-resident.

Applications, with names of 2 referees, to the Administrator.

WELSH REGIONAL HOSPITAL BOARD.

REGISTRAR in anæsthetics, based Bridgend General Hospital. Hospital recognised for F.F.A.R.C.S. Resident/non-resident.

REGISTRAR (general medicine), Swansea General Hospital, Swansea. Non-resident.

SURGICAL REGISTRAR (orthopædics) at Prince of Wales Orthopædic Hospital, Rhydlafar (280 Beds), serving Cardiff Hospital Management Committee. Hospital is Regional Orthopædic Centre for South Wales area. Married accommodation available.

Subject to review end of first year.

Application forms from Senior Administrative Medical Officer, Temple of Peace, Cathays Park, Cardiff, within 14 days.

WEST BROMWICH GROUP OF HOSPITALS. Registrar (Anæsthetics). Duties at Midland Centre for Neurosurgery, Smethwick Hospital and other Group Hospitals. Experience specialty required. Married quarters available.

Application forms from Group Secretary, West Bromwich General Hospital, to be returned by 28th October, 1957.

WOLVERHAMPTON AND MIDLAND COUNTIES EYE INFIRMARY. SENIOR HOUSE OFFICER required. 100 Bed and busy Outpatient Department. Recognised for F.R.C.S. and D.O. examinations.

Applications to Secretary as soon as possible.

YORK. FAIRFIELD SANATORIUM (68 Beds), CITY HOSPITAL (256 Beds). Required in December, 1957, SENIOR HOUSE OFFICER in Chest Diseases and General Medicine (non-resident) to spend half time at Fairfield Sanatorium (68 Beds) and at the City Hospital where 8 beds are reserved for investigation of chest cases, and where outpatient refill clinics are held, and remainder of time at the County and City Hospitals (266 and 256 Beds respectively) in the Department of General Medicine. Previous experience in treatment of tuberculosis an advantage.

Applications, giving age, nationality, experience, qualifications and names of 2 referees, to Group Secretary, York A and Tadcaster Hospital Management Committee, Bootham Park, York.

NORTHERN IRELAND HOSPITALS AUTHORITY. Applications are invited for a whole-time post as REGISTRAR in Psychiatry at Purdysburn Hospital, Belfast (a mental hospital). The terms and conditions will be in accordance with the application of the Spens report to Northern Ireland.

Applications to be made on a form obtainable (with further particulars) from the Secretary, Northern Ireland Hospitals Authority, 44–46, Queen-street, Belfast, and to be returned not later than 4th November, 1957.

U.S.A. BETHESDA HOSPITAL, Cincinnati 6, Ohio, U.S.A. INTERNS—Rotation through Obstetrics, Medicine, Pediatrics and Surgery in a 12-month broad teaching programme. We desire applications from graduate medical doctors giving full details in first letter. $210 per month stipend; access to inexpensive meals; furnished room; uniforms; laundry; hospitalisation, and will advance passage one way.

Please apply to the Superintendent.

U.S.A. JEWISH CHRONIC DISEASE HOSPITAL, BROOKLYN, N.Y. Clinical pathology. 1st or 2nd year RESIDENT. Fully approved 800 Bed active research hospital. 250,000 tests annually; includes steroid, enzyme and histochemistry, electrophoresis, hormone assays and radioisotopes.

Apply: Jewish Chronic Disease Hospital, E. 49th St. and Rutland-road, Brooklyn, N.Y.

DUBLIN. ROYAL VICTORIA EYE AND EAR HOSPITAL. OPHTHALMIC HOUSE SURGEON required for duties at the above Hospital. Appointment for 1 year from 1st January, 1958. Salary £275 p.a.

Applications, with testimonials, to be forwarded to the Registrar before 8th November, 1957.

IBADAN, NIGERIA. UNIVERSITY COLLEGE HOSPITAL. The Board of Management invite applications from medical practitioners with the requisite postgraduate experience and qualifications for the post of SENIOR REGISTRAR (Department of Surgery) in the newly completed Hospital.

The salary offered for the post is: £1428 rising by 3 annual increments of £1596 p.a. plus an inducement addition, payable to an expatriate doctor, of £300 p.a.

Candidates must hold the F.R.C.S. and have had sufficient experience to enable him to deputise for the Consultant. There is plenty of scope for operative experience. SENIOR REGISTRARS, in rotation, supervise the Casualty Department in conjunction with inpatient traumatic work, which is very heavy.

The successful candidate will be expected to assume duty about 1st January, 1958.

The appointment will be initially for one tour of 12 months and will be renewable by mutual agreement for a further tour of 12 months.

On satisfactory completion of the agreement a gratuity of £37 10s. will be paid for each completed term of 3 months' service.

An outfit allowance of £60 is payable on first appointment.

Partly furnished quarters are provided at a rental of 8½% of salary excluding inducement allowance and the officer appointed will be eligible for 7 days' leave on full pay for each completed month of service in Nigeria.

Free first-class passages are provided for expatriate doctors and their wives on first appointment and on completion of the agreement. Free first-class passages to Nigeria will, in certain circumstances, be provided for non-expatriate doctors. Free first-class passages will be provided for vacation leave.

Candidates will be eligible for children's allowances in accordance with existing regulations.

Arrangements can be made to enable doctors to continue their National Health Service superannuation scheme contributions and details of the revised salary and gratuity payable in such cases will accompany application forms.

Applications should be submitted not later than 2nd November, 1957, on the appropriate forms, which will be forwarded, together with additional information on receipt of an addressed foolscap envelope by the Adviser on Staff Recruitment, London Office, University College Hospital, Ibadan, 57, Catherine-place, Palace-street, London, S.W.1.

IBADAN, NIGERIA. UNIVERSITY COLLEGE HOSPITAL. Preregistration HOUSE OFFICERS. Postregistration HOUSE OFFICERS. The Board of Management invites applications from Nigerian graduates for vacancies on 1st February, 1958, for House Officers in the newly completed Teaching Hospital.

Preregistration candidates must be provisionally registered medical practitioners and should be prepared to serve in any of the following Departments: Medicine, Surgery, Obstetrics, and Pædiatrics.

Postregistration candidates must be fully registered medical practitioners and should be prepared to serve in any of the following Departments: Medicine, Surgery, Obstetrics, Pædiatrics, Anæsthetics and General Outpatients.

The appointments will be for 1 tour of 12 months, 6 months to be spent in each of 2 departments, as far as possible, in accordance with the candidates' preference.

The salaries offered for the posts are:—

Preregistration House Officer, £660 p.a.

Postregistration House Officer, £972 p.a.

In addition, a Postregistration House Officer will receive a gratuity, on satisfactory completion of contract, of £25 for each completed term of 3 months' service.

An outfit allowance of £60 is payable on first appointment. Partly furnished quarters are provided at a rental of 8½% of salary. Leave is granted at the rate of 5 days for each completed month of service.

Free first-class passages to Nigeria will be arranged, if not provided by any other authority.

Applications should be submitted to the Adviser on Staff Recruitment, London Office, University College Hospital, Ibadan, 57, Catherine-place, Palace-street, London, S.W.1, not later than 2nd November, 1957, from whom the appropriate forms and additional information can be obtained.

4 Public Appointments

NAVY, ARMY AND AIR FORCE INSTITUTES. Applications are invited from general practitioners in the undernoted towns for the appointment in a part-time capacity as MEDICAL OFFICERS to this Corporation. Successful applicants would be required to examine and report on the condition of employees of the Corporation who may be referred to them from time to time. Fees for this work will be paid on a scale agreed with the British Medical Association.

Applications, giving details of qualifications and experience, should be sent to the Chief Medical Officer, Navy, Army and Air Force Institutes, Kennington-lane, London, S.E.11, not later than 26th October, 1957.

The towns for which applications are invited are:—

DONCASTER	LEEDS	YORK	HULL
HARROGATE	NEWCASTLE	CARLISLE	PENRITH

HER MAJESTY'S OVERSEAS CIVIL SERVICE. Uganda. MEDICAL OFFICERS with qualifications registrable in the United Kingdom required for general duties. Successful candidates may be posted to any station in Uganda. During earlier years of service an officer will be expected to carry out general medical and surgical duties including a varying amount of public health administration and the training of subordinate African medical staff. In most stations, even if remote from large towns, it is possible to maintain interest in any particular branch of medicine or surgery to which the officer is attracted. In most stations the work is based on a district hospital which may vary in size from a comparatively small hospital meeting the needs of a backward community to a large hospital with modern facilities where specialisation in the different branches of medicine, surgery and obstetrics is possible. Appointments can be on permanent basis, subject to 2 years probation, with pension (non-contributory) or on 30–36 months contract with gratuity (taxable) payable on satisfactory completion of service. Normal retiring age is 55 but at age 45 officers may retire with full pension earned. Gratuity for contract service is 13½% of total salary drawn, not including allowances. Candidates from National Health Service may retain superannuation rights up to 6 years and receive gratuity (taxable) of 20% of their salary after engagements. Salary ranges from £1284 to £2115. Starting point determined by experience. 4 extra increments can be given to successful candidates possessing F.R.C.S., M.R.C.P. and D.P.H., and other approved higher qualifications. Other allowances in accordance with current regulations. Permanent Medical Officers are eligible to be considered for promotion to super-scale posts in Uganda and other territories in medical administration or, if they possess higher qualifications and suitable experience, in specialist posts. Quarters provided at rental varying from £21 to £60 according to size and type, and hard furniture at a rate of £12–£24 according to scale. Free air passages for each journey are provided up to equivalent of 4 adult tourist class air fares for Officer, wife and dependent children. If, in the interest of Government an Officer is required to proceed on leave after a short tour of 15–18 months, there is no limit to the number of family passages. Taxation at East African rates, generous home leave granted after each tour in addition to which casual leave is allowed at the rate of 16 days p.a. Primary educational facilities available in all the larger stations. Education subsidies are payable to Officers, which vary from £90 a year (or half the school fees, whichever is less), for primary education for first child, to £190 a year (or three-fifths of school fees, whichever is less) for secondary education for each of second and subsequent children.

Application forms obtainable from Director of Recruitment, Colonial Office, London, S.W.1 (quoting No. BCD.117/9/02).

REGIONAL MEDICAL HEALTH OFFICERS

required by

SASKATCHEWAN DEPARTMENT OF PUBLIC HEALTH

Salary range: $771–$924 per month.

Requirements: Graduation from an approved school of medicine and some medical and administrative experience. Diploma or Masters degree in Public Health desirable but not essential. To do professional medical and administrative work as Medical Health Officers in organised health regions, with populations of approximately 50,000 and to develop regional preventive health services and a general public health programme.

Benefits: 3-weeks holiday and 3-weeks accumulative sick leave annually with pay, generous pension plan and opportunity for assisted postgraduate training.

Applications: Forms and further information available at PUBLIC SERVICE COMMISSION, Legislative Building and Department of Public Health, Provincial Health Building, Regina, Sask., Canada. Applicants should refer to file No. 5024.

FACTORY DOCTORS. Factories Acts, 1937 and 1948. The following appointments as Appointed Factory Doctor are vacant. Apply to Chief Inspector of Factories, 19, St. James's-square, London, S.W.1:—

District	*County*	*Latest date for receipt of applications*
NEWCASTLE-ON-TYNE	NORTHUMBERLAND	9TH NOVEMBER, 1957
GLASGOW WEST	LANARK	9TH NOVEMBER, 1957

BUCKS COUNTY COUNCIL. Applications are invited from registered medical practitioners for the appointment of ASSISTANT COUNTY MEDICAL OFFICER (Female) in the High Wycombe area. Preference will be given to applicants possessing a Diploma in Public Health or a Diploma in Child Health, and experience in maternity, school medical and child welfare work. Salary within the scale £1050–£1475 p.a., the commencing salary being fixed according to qualifications and experience. Travelling and subsistence allowances on the County Council's scale will be paid. The appointment is superannuable and subject to medical examination.

Further particulars and forms of application may be obtained from the County Medical Officer, County Offices, Aylesbury, to whom completed applications must be returned by 9th November, 1957.

R. E. MILLARD, Clerk of the Bucks County Council.

County Hall, Aylesbury, October, 1957.

LANCASHIRE COUNTY COUNCIL. Applications are invited from registered medical practitioners for appointment as ASSISTANT DIVISIONAL MEDICAL OFFICERS in the County area north west of Oldham and in the vicinity of Liverpool and Warrington. Possession of Diploma in Public Health desirable. Salary £1050 rising to £1475 p.a. Travelling and subsistence allowances where applicable.

Application forms and further particulars from County Medical Officer, Serial 454, East Cliff County Offices, Preston. Application forms to be returned by 26th October, 1957.

WEST HAM. COUNTY BOROUGH OF WEST HAM. ASSISTANT MEDICAL OFFICER (Administrative). Applicants must be registered medical practitioners holding D.P.H., D.C.H. and/or D.Obst.R.C.O.G. also an advantage. Duties mainly administrative, to assist the Senior Medical Officers, mainly in Maternity and Child Welfare and School Health. At least 2 or 3 years experience of School Health and Maternity and Child Welfare essential. Salary scale £1050–£50 (3)–£55 (5)–£1475 p.a. Starting point according to qualifications and experience.

Further particulars from Medical Officer of Health, 225, Romford-road, Forest Gate, E.7, to whom applications are returnable by 28th October, 1957.

GOVERNMENT OF ADEN PROTECTORATE. Applications invited from Doctors with medical qualifications registrable in United Kingdom for following posts of a pioneering nature, in Aden Protectorate Health Service.

OPHTHALMOLOGIST to be based on Makhzan, Western Aden Protectorate, where there is a developing Base Hospital and a Health Service Training Centre, but about half time to be spent on tour in both Western and Eastern Protectorates, working in Hospitals, Health Units in the field, and training subprofessional staff in simple eye work. Private practice allowed, but very limited. Candidates must possess D.O.M.S. or equivalent, and practical experience. Knowledge of Arabic an advantage.

WOMAN MATERNITY AND CHILD HEALTH SPECIALIST to be based on Mukalla, Eastern Aden Protectorate, where there is a developing Base Hospital and a Health Services Training Centre, but about half time to be spent on tour in both Protectorates, working in Hospitals, Health Units in the field, and training sub-professional staff in nursing, midwifery and M.C.H. work generally, including home visiting. There will be a Matron colleague. Candidates must possess special qualifications in gynæcology, obstetrics and child health and/or practical experience in these subjects, of wide coverage in both competence and responsibility.

Appointments on contract for 1 tour of 18-24 months in the first instance with gratuity (taxable) of £37 10s. for each completed 3 months of service, payable on satisfactory completion of contract. Salary for Ophthalmologist £2000 a year. For M.C.H. Specialist with M.R.C.O.G., £2000; without M.R.C.O.G., £1750. Following allowances also payable:

(*a*) Outfit allowance, £60.

(*b*) Education allowance for children between 8–18 undergoing full-time education outside Aden.

Furnished quarters being built at low rental. Income tax at local rates. Free passages for officer, wife and up to 3 to 4 children under age 18. Generous home leave after each tour.

Application forms from Director of Recruitment, Colonial Office, London, S.W.1 (quoting BCD 117/2/010).

GOVERNMENT OF NORTHERN RHODESIA. Medical OFFICER required for Pneumoconiosis Medical and Research Bureau. Duties include clinical and radiological examination of miners (European and African). Officer will be stationed at Kitwe and will work under supervision of Chairman (a Medical Specialist) of the Bureau. Kitwe is a town of considerable size with agreeable climate and many social amenities. Post offers excellent opportunity for experience in diseases of chest and research in pneumoconiosis. Appointment on permanent basis with pension, or short-term contract with gratuity (taxable). Candidates from National Health Service may retain superannuation rights (up to 6 years) and receive gratuity (taxable) of 20% of aggregate of salary at end of engagement. Salary scale £1245 to £2030 a year, starting salary depending upon age and experience. Pension for permanent appointment at rate of 1/600th of final pensionable emoluments for each completed month of service. Gratuity for contract appointment £37 10s. for each completed 3 months of service. Free passages provided in both directions for officer and wife, and assisted passages for children. Housing available and married candidates may take family. Candidates (Male only) should be aged 25 to 35, possess medical qualifications registrable in United Kingdom and have had at least 12 months post-graduate experience.

Application forms from Director of Recruitment, Colonial Office, London, S.W.1 (quoting BCD 117/3/02).

HER MAJESTY'S OVERSEAS SERVICE. Tanganyika. MALE MEDICAL OFFICERS, with qualifications registrable in United Kingdom, required for general duties. Officers would normally be based on a Hospital, but must be prepared to tour and to train African staff. Professional work covers a wide field in all branches of medicine, surgery and obstetrics with unusual responsibility and scope for initiative. Ample opportunities for sport and recreation. Limited private practice is at present permitted. Appointment can be made on permanent basis with pension (non-contributory), or on short-term contract with gratuity (taxable) on satisfactory completion of service. National Health Service Doctor may retain superannuation rights (up to 6 years) and receive gratuity (taxable) of 20% of aggregate salary after engagement. Salary ranges from £1284 to £2115 a year, starting point determined by experience. Four extra increments given for approved higher qualifications. Permanent officers can be members of Her Majesty's Overseas Civil Service and are eligible to be considered at any time for promotion to higher salaried posts in Tanganyika and other territories in medical administration or, if they possess higher qualification and suitable experience, in specialist posts. Quarters generally available at rental of £30 to £78 a year according to size and type, furniture £12 to £24 a year. Free passages in both directions for officer and wife and up to cost of 1 adult fare for children. Taxation at local rates. Annual local leave permissible and generous home leave after each tour of from 30 to 36 months. Educational facilities.

Application forms from Director of Recruitment, Colonial Office, Great Smith Street, London, S.W.1 (quoting BCD.117/8/02).

HER MAJESTY'S OVERSEAS CIVIL SERVICE. WINDWARD ISLANDS. DISTRICT MEDICAL OFFICERS required for general duties in Dominica, with liability for service in any Institution, Dispensary, or District within the Windward Islands. Candidates must hold qualification registrable in United Kingdom. Appointment on permanent basis with pension (non-contributory) or on agreement for 3 years. Salary scale £800 to £1000 a year. Pay addition of 20% of salary also payable. Pension 1/600th of final pensionable emoluments for each completed month of service. Income tax at local rates. Private practice if duties permit, but all fees for medical attention at Dispensary or Institution accrue to Government. Quarters not normally provided, but if Government quarters become available rental of 10% of salary, or 5% of assessed value of quarters, whichever is less, will be charged. Free passages on appointment for officer, wife and dependent children under 18 years, not exceeding 5 persons in all. If appointed on contract, free return passages on completion of contract. Leave passages in accordance with Windward Islands Regulations.

Application forms from Director of Recruitment, Colonial Office, London, S.W.1 (quoting BCD 117/40/01).

Miscellaneous

RESEARCH PHARMACOLOGISTS

BENGER LABORATORIES LIMITED, manufacturers of ethical medical preparations, have vacancies in their laboratories offering considerable scope for advancement for Research Pharmacologists, both graduate and non-graduate.

Applications are invited from University graduates in Physiology, Pharmacology or Zoology, most particularly from those having a special interest in experimental surgery. Non-graduate laboratory assistants with previous experience in Pharmacology are also required.

The work, which is carried out in close co-operation with other members of the Pharmacology and Biochemistry Research Sections, is extremely interesting and varied. Every encouragement and opportunity is given for the display of initiative and originality.

The salary will depend very much on the experience, qualifications and age of the applicant, but a wide range is contemplated. A Contributory Pension Scheme is in operation.

The well-equipped laboratories are set in ideal country surroundings and there are good facilities available for sport and recreation.

Applications, which will be dealt with in strict confidence, should be addressed to the Secretary, Benger Laboratories Limited, Holmes Chapel, Cheshire.

Birmingham Family Planning Association Clinic. 14, Frederick-road, Edgbaston, Birmingham, 15. Applications are invited for the post of Medical Officer (Male) interested in marital problems, to conduct the Men's Clinic on one evening fortnightly.

Applications to the Hon. Secretary, by 9th November, from whom further details may be obtained.

Calmic Limited require the services of a Technical Executive to control the development of medical preparations intended for home and established overseas markets. Successful applicant will be required to take charge of the research, analytical and biochemical laboratories. Medical qualifications essential and clinical experience desirable.

Please give full particulars of experience, salary required and references, to Managing Director, Calmic Limited, Crewe Hall, Crewe.

Applicants for posts requiring testimonials copied or duplicated should communicate with MANTON SECRETARIAL SERVICE LTD., 98, Victoria-street, S.W.1 (Phone: VICtoria 0141), who are specialists in this kind of work.

For Sale. Microscope. Leitz. 2/3, 1/6, oil immersion specimen. £20 o.n.o.—Dr. JENSEN, Plas Uchaf-avenue, Prestatyn.

Doctors requiring applications, theses copied: Write to MANTON (WESTMINSTER) LTD., 98, Victoria-street, S.W.1 (VIC 0141) who are specialists.

A Doctor's Residence to be built on excellent site amidst extensive new estate developments at Hornchurch. The plot is approximately 40 ft. by 200 ft. in size. (Price £1500 freehold.) Design to purchaser's choice. For further details please call or write.—Sole Agents, ANDREWS & PARTNERS, 139/143, Oxford-street, W.1 (opposite Bourne & Hollingsworth). Tel.: GERrard 1555/6/7.

Government Surplus. 25,000 new white operation gowns, 6000 new white 3-pint china basins packed in cases (20 in case), 3500 new linen hospital masks, 1000 new green baize aprons, 750 new hospital flannel shirts.—Write: BASSETT, 331, Kingsland-road, E.8 (Phone: CLIssold 7037).

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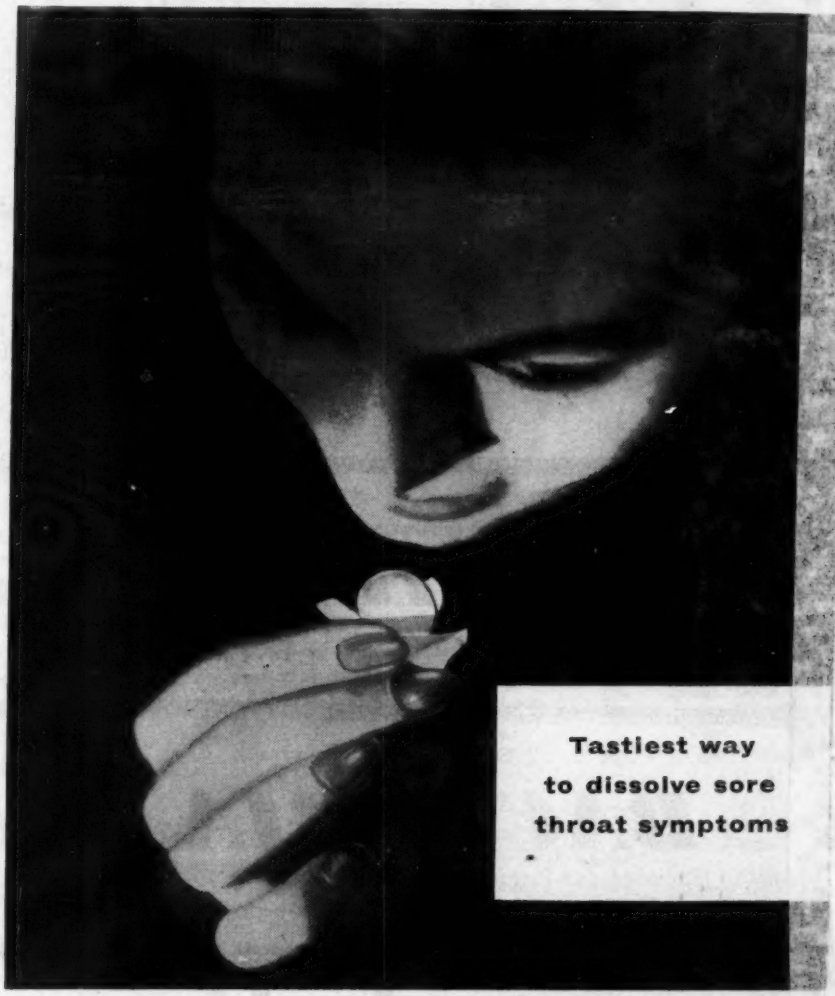

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